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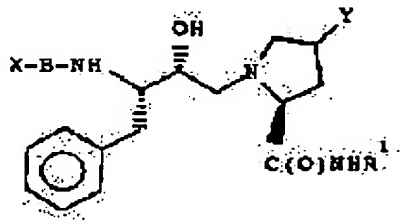
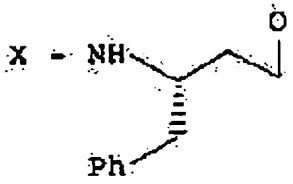
(54) SUBSTITUTED PYRROLIDINE DERIVATIVE AND HIV PROTEASE INHIBITOR

(57)Abstract:
PURPOSE: To obtain compounds having inhibiting activity of human immunodeficiency virus protease, which are useful in the treatment of HIV infections.
CONSTITUTION: Compounds of formula I [X is an R2OD(O), R2NR3C(O) or the like; R2 is a lower alkyl, phenyl or the like; R3 is H or a lower alkyl; R1 is a lower alkyl or lower cycloalkyl; Y is a lower alkyl, lower cycloalkyl, phenyl or the like; B is absent or a divalent group -NHCHR4C(O)-; R4 is a lower alkyl or the like], such as 4(S)-benzyloxy-1{3(S)-{[N-(benbyloxyloxycarbonyl)-valyl]amino}-2(R)-hydroxy-4-phenylbutyl}-N-tert-butylpyrrolidine-2(S)- carboxamide. The compd. of the formula I is obtained by reacting an epoxide of the formula II with pyrrolidinecarboxamide of formula III.



I



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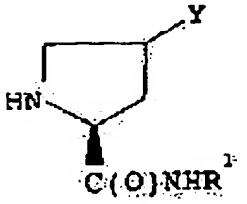


III

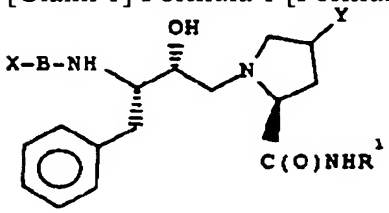
LEGAL STATUS
[Date of request for examination] 15.03.2000

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] Formula 1 [Formula 1]



1

The compound come out of and shown, or its acid addition salt which may be permitted in thrapeutics. [-- however, the inside of a formula and X -- R2 OC (O), R2 C (O), or R2 NR3 C (O) -- it is (R2 among a formula) (i) Low-grade alkyl and (ii) low-grade cycloalkyl, phenyl (iii), or a halogen, The phenyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI, (iv) Phenyl (low-grade) alkyl or its aromatic series part Halogen, The phenyl (low-grade) alkyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI, (v) 1-naphthyl or 2-naphthyl, (vi) (Het), or (Het) - (low-grade alkyl) (Het) Or the univalent heterocycle radical of 5 containing the hetero atom of 1 or 2 chosen from nitrogen, oxygen, or sulfur or 6 members is shown (vii), they are 2-kino RINIRU or 3-kino RINIRU. And; or X whose R3 is hydrogen or low-grade alkyl It is R2AOCH2 C (O) (R2A among a formula). ;B which is one permutation, two permutations, or the phenyl carried out 3 ****s with phenyl, low-grade alkyl, or a halogen They are whether it exists and divalent radical-NHCHR4 C(O)- (among a formula). R4 hydroxy ** low-grade alkyl; -- low-grade cycloalkyl; (low-grade cycloalkyl) -(low-grade alkyl); phenylmethyl; -- or it is the low-grade alkyl carried out by 1 **** of carboxy, low-grade alkoxy carbonyl, aminocarbonyl, aminocarbonyl (low-grade alkyl), or JI (low-grade alkyl) aminocarbonyl --;R1 They are low-grade alkyl or low-grade cycloalkyl.;Y hydroxy ** low-grade alkyl; -- low-grade -- cycloalkyl; phenyl or a halogen -- Phenyl carried out by 1 **** of low-grade alkyl or low-grade ARUKOKISHI; Phenylmethyl or a halogen, It is phenylmethyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI.; or Y It is W(CH2) n Z (W is oxo-** thio, sulfinyl, or a sulfonyl among a formula Z). low-grade -- phenyl; carried out by 1 **** of alkyl; phenyl or a halogen, hydroxy ** low-grade alkyl, or low-grade ARUKOKISHI -- or (Het) -- it is (the inside of a formula and (Het) are as the above-mentioned definition) --;n is 0 or 1.] .
[Claim 2] The inside of a formula and X are R2 OC (O) or R2 C (O) (R2 among a formula). low-grade -- alkyl; phenyl (low-grade) alkyl; -- phenyl (low-grade) alkyl (the 4th place of a phenyl part -- chloro --) ; or X which is the;1-naphthyl;2-naphthyl;2-furil;2-thienyl;2-pilus JINIRU;4-pilus JINIRU;2-pilus JINIRU methyl;4-thiazolyl methyl or 2-kino RINIRU permuted by fluoro, hydroxy ** methyl, or methoxy It is R2AOCH2 C (O) (R2A among a formula). In the location or two or more locations of 1 chosen from the group which consists of phenyl or 2 and 4, and the 6th place,;B which is 1, 2, or the phenyl carried out 3 ****s with low-grade alkyl or a halogen It does not exist or is divalent radical-NHCHR4 C(O)- (R4 among a formula). Low-grade alkyl or hydroxy ** low-grade alkoxy carbonyl, aminocarbonyl, (Low-grade alkyl) it is the low-grade alkyl carried out by 1 **** of aminocarbonyl or JI (low-grade alkyl) aminocarbonyl --;R1 They are 1-methylethyl, 1, and 1-dimethyl ethyl, 2-methylpropyl, cyclo propyl, cyclo butyl, cyclopentyl, or cyclohexyl.;Y Low-grade cycloalkyl, phenyl, 4-chlorophenyl, 4-BUROMO phenyl, 4-fluoro phenyl, 4-methylphenyl, 4-methoxypheny, phenylmethyl, methyl (4-fluoro phenyl), or (4-methylphenyl) methyl -- it is --; -- or -- Y It is W(CH2) n Z (W and n are as the above-mentioned definition among a formula). Z Low-grade alkyl, phenyl, 2-furil, 2-thienyl, 2-pyridinyl The compound according to claim 1 which is 3-pyridinyl

4-pyridinyl 4-thiazolyl, 2-pyrimidinyl, 4, and 6-dimethyl-2-pyrimidinyl or 2, and 6-dimethyl-4-pyrimidinyl, or its acid addition salt which may be permitted in thrapeutics.

[Claim 3] X among a formula tert-butyloxy carbonyl, benzyloxycarbonyl, Methoxycarbonyl, methoxycarbonyl (4-hydroxyphenyl), (4-chloro-phenyl) Methoxycarbonyl, acetyl, benzoyl, (4-methoxypheny) 1-North America Free Trade Agreement RENIRU carbonyl, 2-North America Free Trade Agreement RENIRU carbonyl, 2-pilus JINIRU methoxycarbonyl, or 2-KINORI nil carbonyl, Phenoxy acetyl, acetyl (2-methylphenoxy), acetyl (2, 4-dimethyl phenoxy), (2 and 6-dimethyl phenoxy)-acetyl, acetyl (2, 4, 6-trimethyl phenoxy), They are acetyl or (the 4-fluoro -2, 6-dimethyl phenoxy) acetyl. (4-chloro phenoxy);B It does not exist or is divalent radical-NHCHR4 C(O)- (R4 among a formula). 1-methylethyl, 1, and 1-dimethyl ethyl, 1-methylpropyl, they are 2-methylpropyl, methoxy carbonylmethyl, ethoxycarbonyl-methyl, or aminocarbonyl methyl --;R1 They are 1 and 1-dimethyl ethyl or cyclo propyl.;Y Cyclohexyl, phenyl, 4-chlorophenyl, 4-fluoro phenyl, 4-methoxypheny, benzyl, methyl (4-methoxypheny), 2-methyl propoxy, phenoxy, and 2-pilus JINIRU oxy-**3-pilus JINIRU oxy-** 4-pilus JINIRU oxy-**2-pyrimidinyl oxy-**4 and 6-dimethyl-2-pyrimidyl oxy-** 2, 6-dimethyl-4-pyrimidinyl oxy-** benzyloxy, 2-pilus JINIRU methoxy, 4-thiazolyl methoxy, 2-pyrimidinyl methoxy, phenylthio, Phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, 4, 6-dimethyl thio-2-pyrimidinyl thio, benzyl thio, benzyl sulfinyl, The compound according to claim 2 which is a benzyl sulfonyl, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or (4-pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 4] X among a formula tert-butyloxy carbonyl, benzyloxycarbonyl, They are acetyl, 2-North America Free Trade Agreement RENIRU carbonyl, 2-pilus JINIRU methoxycarbonyl, and 2-KINORI nil carbonyl.; B It is the valyl, the isoleucyl, or the asparaginyl and is;R1. They are 1 and 1-dimethyl ethyl or cyclo propyl.;Y Phenyl, benzyl, phenoxy, 2-pyrimidinyl oxy-**2, and 6-dimethyl-4-pyrimidinyl oxy-** Benzyloxy one, phenylthio, a phenyl sulfonyl, 2-PIRIJI nil thio, The compound according to claim 3 which is 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, 4, and 6-dimethyl-2-pyrimidinyl thio or (3-pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 5] X among a formula Acetyl (2-methylphenoxy), (2 and 4-dimethyl phenoxy)-acetyl, (2, 6-dimethyl phenoxy) It is acetyl or (2, 4, 6-dimethyl phenoxy) acetyl, and;B does not exist, but it is;R1. It is 1 and 1-dimethyl ethyl.;Y Phenyl, benzyl, phenoxy, 2-pyrimidinyl oxy-**2, and 6-dimethyl-4-pyrimidinyl oxy-** Benzyloxy one, phenylthio, a phenyl sulfonyl, 2-PIRIJI nil thio, The compound according to claim 1 which is 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, 4, and 6-dimethyl-2-pyrimidinyl thio or (3-pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 6] four -- (-- S --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- four -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- four -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- four -- (-- S --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N - tert - butyl - four -- the (S)-2-methylpropyl oxy-pyrrolidine-2(S)-carboxamide -- one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert -- the - butyl-4(R)-(2-methylpropyl oxy-) pyrrolidine-2(S)-carboxamide -- four -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N - cyclo -- propyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- the 4(R)-benzyl -1 - {3(S)-{{N-(benzyloxycarbonyl) asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl --} -- the -N-tert-butyl pyrrolidine-2(S)-carboxamide -- the 4(S)-benzyl -1 - {3(S)-{{N-(benzyloxycarbonyl) asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl --} -- the -N-tert-butyl pyrrolidine-2(S)-carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a pyrrolidine - two -- (-- S

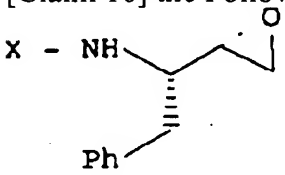
--) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2, 6-dimethyl-4-pyrimidinyl) -- oxo-one --} -- a pyrrolidine - two -- (-- S --) - the carboxamide -- N-tert-butyl -1 - {3(S)-{{(2, 6-dimethyl phenoxy) - acetyl} amino}-2(R)-hydroxy-4-phenyl butyl --} -4 (R) -- the -2-pyrimidinyl thio-pyrrolidine-2(S)-carboxamide -- And N-tert-butyl-1-{3 (-- S --) - {-- {-- two -- six - dimethyl -- phenoxy -- acetyl --} - amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a pyrrolidine - two -- (-- S --) - the carboxamide -- from -- becoming -- a group -- from -- choosing -- having -- being according to claim 1 -- a compound .

[Claim 7] The pharmacological constituent containing a compound according to claim 1 or its salt which may be permitted in thrapeutics, and the support which may be permitted pharmacologically.

[Claim 8] How to treat a human HIV infectious disease including medicating Homo sapiens with the compound or its salt which may be permitted in thrapeutics of an effective dose according to claim 1.

[Claim 9] How to protect the cell of Homo sapiens including processing a human cell by the compound or its salt which may be permitted in thrapeutics of an anti-HIV effective dose according to claim 1 from a HIV pathogen.

[Claim 10] the Following Process:(a) type 2 -- [Formula 2]



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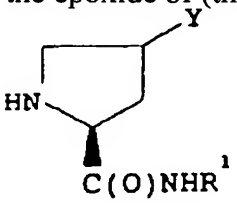
the epoxide of (the inside of a formula and X are as having defined claim 1), and a formula 3 -- [Formula 3]



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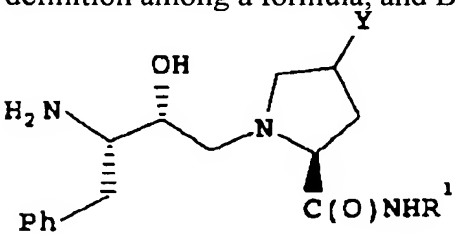
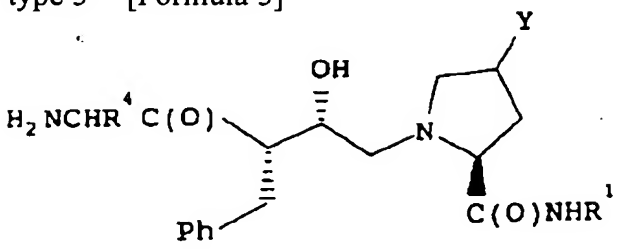
or [obtaining the compound with which the pyrrolidine carboxamide of (the inside of a formula, R1, and Y are as having defined claim 1) is made to react, and a formula 1 (X, R1, and Y are as the above-mentioned definition among a formula, and B does not exist) corresponds] --; or the (b) type 4 -- [Formula 4]



4

It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, and Y are as the above-mentioned definition). The reactant derivative of being R2 C (O) or R2AOCH2C (O) defined in claim 1 is made to react. Formula 1 (X is R2 C [of the above-mentioned definition] (O), or R2AOCH2 C (O) among a formula) The corresponding compound with which R1 and Y are as the above-mentioned definition, and B does not exist is obtained, or they are; or the (c) type 4 (R1 and Y among a formula). The compound and formula X-NHCHR4 COOH (X and R4 among a formula) of being as the above-mentioned definition Coupling of the alpha-amino acid of being as the definition of claim 1 is carried out under existence of a coupling agent, and it is a formula 1 (X, R1, and Y among a formula). or [obtaining the corresponding compound of it being as the above-mentioned definition and B being divalent radical-NHCHR4 C(O)- (the inside of a formula and R4 being as the above-mentioned definition)] --; or the (d)

type 5 -- [Formula 5]



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It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R4, and Y are as the above-mentioned definition). The reactant derivative of being R2 C (O) of the above-mentioned definition or R2AOCH2 C (O) is made to react, and it is a formula 1 (X). It is R2 C (O) of the above-mentioned definition, or R2AOCH2 C (O), and is R1. And Y the corresponding compound of it being as the above-mentioned definition and B being divalent radical-NHCHR4 C(O)- (the inside of a formula and R4 being as the above-mentioned definition) -- obtaining --; -- subsequently (e) How to manufacture the compound or the acid addition salt which may be permitted in thrapeutics including changing the compound of the formula 1 obtained by the request in the above-mentioned section (a), (b), (c), or (d) into the corresponding acid addition salt which may be permitted in thrapeutics of the formula 1 according to claim 1.

[Translation done.]

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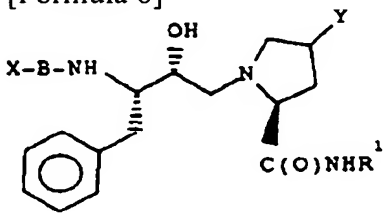
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the operation of the compound which repulses the infectious disease produced by the compound in which the activity over a specific retrovirus is shown, the manufacture approach of the compound, its pharmacological formula object, and the retrovirus.
[0002]
[Description of the Prior Art] The retrovirus known as a human immunodeficiency virus type 1 (HIV-1) in 1983 was established as a pathogen of acquired immunodeficiency **** (acquired immunode-ficiency syndrome). R.C. Galo and "Scientific American" by L. MONTANI yell, 259 (4), 40 (1988) reference. This virus serves as an epidemic like making fear have. Recently, the virus and the human immunodeficiency virus type 2 (HIV-2) which are related very much are identified more as the 2nd pathogen of an acquired immunode-ficiency syndrome. The compound which checks the duplicate of HIV in the outside of a living body is discovered by identifying the human immunodeficiency virus (HIV) as a pathogen, and developing the approach of growing up this virus in large quantities. the most important class of inhibition compound identified by this approach -- the group of a dideoxy nucleoside -- it is -- that 3 '- azide -3'-deoxythymidine (known also as zidovudine or AZT) -- and more, 2'3'-dideoxyinosine (known also as didanosine or DDI) is used in thrapeutics, and, recently, has managed the specific patient according to a **** HIV infectious disease. When this kind of compound checks reverse transcription, barring the life cycle of HIV is discovered. This enzyme converts Virus RNA into a double strand deoxyribonucleic acid (DNA), and is an indispensable enzyme for a HIV duplicate in itself. Besides inhibition of reverse transcription, the term of others of a HIV life cycle is identified as a target for development of anti-HIV medicine. The target of 1 which has received increasing cautions is an enzyme which is known as a HIV protease and by which the HIV code was carried out. Like reverse transcriptase, the code of this enzyme is carried out by the pol gene, and it is indispensable to growth of HIV. This is a causative agent which emits the enzyme containing the structural protein (for example, p17 and p24) and itself which perform specific division in gag or (p55) gag-pol protein (p180), and are seen in mature infectivity virion. Therefore, the inhibitor of a HIV protease can block a HIV life cycle.
[0003] The increment in the interest with which the HIV protease was filled is reflected in the increment in a report of discovery of the matter which checks an enzyme over the past several years. For example, refer to the paper of the bacteria about D.W. Nor Bec and D.J. kemp, "Annual Reports In Medicinal Chemistry", and the protease inhibitor by 26,141 (1991). As the latter paper is indicated and it is reported by J. D.H. Rich et al., "Med.Chem.", 33 and 1285 (1990) and N.A. Roberts et al., "Science", and 248 and 358 (1990) Two powerful HIV protease inhibitor systems are understood by arranging a hydroxy ethylamine transition state prototype (TSA) in the peptide which has p17 / p24 substrate decomposition part array. biological research of the lead compound of continuation of Roberts and others -- H.A. exaggerated tons, "Virology", 179 and 508 (1990), J.A. Martin et al., and "Biochem.Biophys.Res.Commun." -- it is reported by 176, 180 (1991) and J.C. Craig et al., "Antiviral Chemistry and Chemotheraphy", and 2,181 (1991). An indication of others of the HIV protease inhibitor which has the hydroxy ethylamine TSA : which includes the following -- B.K. pewters and the Europe patent application No. 346847 published on December 20, 1989 G. B. DOREIYA et al., Europe patent application No. 352000 published on January 24, 1990, D. J. kemps, Europe patent application No. 402646 published on December 19, 1990, K -- the E.B. Per Cars et al., the Canadian patent application No. 2,030,415 published on June 12, 1991, J.A. Martin and S. red show, and the Europe patent application No. 432695 published on June 19, 1991.
[0004]

[Elements of the Invention] This application indicates the permutation pyrrolidine derivative which has the ethylamine TSA introduced into the structure. These derivatives are the powerful inhibitors of a HIV protease. Furthermore, the capacity which checks the cytopathogenic effectiveness by which HIV induction was carried out in the human cell is shown about these compounds. Since it has comparatively alternative operation and property that no toxicity is clearly, in these property lists, the compound is effective as drugs for repulsing a HIV infectious disease. The compound of this invention is a formula 1 [0005].
[Formula 6]



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[0006] It is the acid addition salt which comes out, is shown or may be permitted in thrapeutics. However, the inside of a formula and X are R2 OC (O), R2 C (O), or R2 NR3 C (O) (R2 among a formula). (i) Low-grade alkyl and (ii) low-grade cycloalkyl, phenyl (iii), or a halogen, The phenyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI, (iv) Phenyl (low-grade) alkyl or an aromatic series part A halogen, hydroxy ** The phenyl (low-grade) alkyl carried out by 1 **** of low-grade alkyl or low-grade ARUKOKISHI, (v) 1-naphthyl or 2-naphthyl, (vi) (Het), or (Het) - (low-grade alkyl) (Het) The univalent heterocycle radical of 5 containing the hetero atom of 1 or 2 chosen from nitrogen, oxygen, and sulfur or 6 members is shown. or (vii) 2-kino RINIRU or 3-kino RINIRU -- it is -- R3 [and] ; or X which is hydrogen or low-grade alkyl is R2AOCH2 C (O) (inside of formula and R2A is one permutation, two permutations, or the phenyl carried out 3 ****s by phenyl, low-grade alkyl, or the halogen).;
[0007] B is whether it exists and divalent radical-NHCHR4 C(O)- (among a formula). R4 hydroxy ** low-grade alkyl; -- low-grade cycloalkyl; (low-grade cycloalkyl) -(low-grade alkyl); phenylmethyl; -- or it is the low-grade alkyl carried out by 1 **** of carboxy, low-grade alkoxy carbonyl, aminocarbonyl, aminocarbonyl (low-grade alkyl), or JI (low-grade alkyl) aminocarbonyl --;R1 They are low-grade alkyl or low-grade cycloalkyl.;Y hydroxy ** low-grade alkyl; -- low-grade -- cycloalkyl; phenyl or a halogen -- Phenyl carried out by 1 **** of low-grade alkyl or low-grade ARUKOKISHI; Phenylmethyl or a halogen, It is phenylmethyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI.; or Y It is W(CH2) n Z (W is oxo-** thio, sulfinyl, or a sulfonyl among a formula Z). low-grade -- phenyl; carried out by 1 **** of alkyl; phenyl or a halogen, hydroxy ** low-grade alkyl, or low-grade ARUKOKISHI -- or (Het) (the inside of a formula and (Het) are as the above-mentioned definition) -- it is --;n is 0 or 1.
[0008] the phrase "B does not exist" used by this detail letter about a formula 1 should understand that it means that Notation B serves as covalent bond which combines "X" with the 2nd amino group (it combines with "B" in the case of others). The suitable group of the compound of this invention is a formula 1 (X among a formula). They are R2 OC (O) or R2C (O) (R2 among a formula). low-grade -- alkyl; phenyl (low-grade) alkyl; -- phenyl (low-grade) alkyl (the 4th place of a phenyl part -- chloro --) ; or X which is the;1-naphthyl;2-naphthyl;2-furil;2-thienyl;2-pilus JINIRU;4-pilus JINIRU;2-pilus JINIRU methyl;4-thiazolyl methyl or 2-kino RINIRU permuted by fluoro, hydroxy ** methyl, or methoxy It is R2AOCH2 C (O) (R2A among a formula). In the location or two or more locations of 1 chosen from the group which consists of phenyl or 2 and 4, and the 6th place,;B which is 1, 2, or the phenyl carried out 3 ****s with low-grade alkyl or a halogen It does not exist or is divalent radical-NHCHR4 C(O)- (R4 among a formula). Low-grade alkyl or hydroxy ** low-grade alkoxy carbonyl, aminocarbonyl, (Low-grade alkyl) it is the low-grade alkyl carried out by 1 **** of aminocarbonyl or JI (low-grade alkyl) aminocarbonyl --;R1 They are 1-methylethyl, 1, and 1-dimethyl ethyl, 2-methylpropyl, cyclo propyl, cyclo butyl, cyclopentyl, or cyclohexyl.;

[0009] Y Low-grade cycloalkyl, phenyl, 4-chlorophenyl, 4-BUROMO phenyl, 4-fluoro phenyl, 4-methylphenyl, 4-methoxypheny, phenylmethyl, methyl (4-fluoro phenyl), or (4-methylphenyl) methyl -- it is --; -- or -- Y It is W(CH2) n Z (W and n are as the above-mentioned definition among a formula). Z Low-grade alkyl, phenyl, 2-furil, 2-thienyl, 2-pyridinyl 3-pyridinyl 4-pyridinyl 4-thiazolyl, 2-pyrimidinyl, 4, and 6-dimethyl-2-pyrimidinyl or 2, and 6-dimethyl-4-pyrimidinyl -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics. The more desirable group of the compound of this invention is a formula 1 (X among a formula). tert-butyloxy carbonyl, benzyloxycarbonyl, methoxycarbonyl

(4-chloro-phenyl), Methoxycarbonyl, methoxycarbonyl (4-methoxypheny), (4-hydroxyphenyl) Acetyl, benzoyl, 1-North America Free Trade Agreement RENIRU carbonyl, 2-North America Free Trade Agreement RENIRU carbonyl, 2-pilus JINIRU methoxycarbonyl, 2-KINORI nil carbonyl, phenoxy acetyl, Acetyl, acetyl (2, 4-dimethyl phenoxy), (2-methylphenoxy) They are (2 and 6-dimethyl phenoxy)-acetyl, acetyl (2, 4, 6-trimethyl phenoxy), acetyl (4-chloro phenoxy), or (the 4-fluoro -2, 6-dimethyl phenoxy) acetyl.;

[0010] B does not exist or is divalent radical-NHCHR4 C(O)- (R4 among a formula). 1-methylethyl, 1, and 1-dimethyl ethyl, 1-methylpropyl, 2-methylpropyl, methoxy carbonylmethyl, ethoxy carbonylmethyl, or aminocarbonyl methyl -- it is --;R1 They are 1 and 1-dimethyl ethyl or cyclo propyl.;Y Cyclohexyl, phenyl, 4-chlorophenyl, 4-fluoro phenyl, 4-methoxypheny, benzyl, methyl (4-methoxypheny), 2-methyl propoxy, phenoxy, and 2-pilus JINIRU oxy-**3-pilus JINIRU oxy-** 4-pilus JINIRU oxy-**2-pyrimidinyl oxy-**4 and 6-dimethyl-2-pyrimidinyl oxy-** 2, 6-dimethyl-4-pyrimidinyl oxy-** benzyloxy, 2-pilus JINIRU methoxy, 4-thiazolyl methoxy, 2-pyrimidinyl methoxy, phenylthio, Phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, 4, 6-dimethyl-2-pyrimidinyl thio, benzyl thio, benzyl sulfinyl, a benzyl sulfonyl, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or (4-pilus JINIRU methyl) thio -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics.

[0011] The most desirable group of the compound of this invention is a formula 1 (X among a formula). tert-butyloxy carbonyl, benzyloxycarbonyl, acetyl, They are 2-North America Free Trade Agreement RENIRU carbonyl, 2-pilus JINIRU methoxycarbonyl, or 2-KINORI nil carbonyl.;B the valyl, the isoleucyl, or the asparaginyl -- it is --;R1 They are 1 and 1-dimethyl ethyl or cyclo propyl.; and Y Phenyl, benzyl, phenoxy, 2-pyrimidinyl oxy-**2, and 6-dimethyl-4-pyrimidinyl oxy-** Benzyloxy one, phenylthio, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, 4, and 6-dimethyl-2-pyrimidinyl thio or (3-pilus JINIRU methyl) thio -- it is -- it is the acid addition salt which is shown or may be permitted in thrapeutics. The most desirable group of others of the compound of this invention a formula 1 (the inside of a formula, and X -- acetyl (2-methylphenoxy) and acetyl (2, 4-dimethyl phenoxy) --) Acetyl (2, 6-dimethyl phenoxy) or (2, 4, 6-dimethyl-phenoxy) acetyl -- it is --;B -- not existing --;R1 as being 1 and 1-dimethyl ethyl and having defined; and Y immediately before -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics. It is related with the compound of a formula 1 (the inside of a formula and B are divalent radical-NHCHR4 C(O)-), and is R4. As for the asymmetric carbon atom to support, it is desirable to have (S) arrangement.

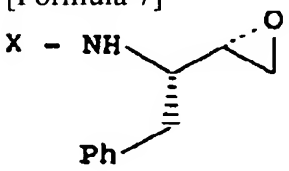
[0012] The pharmacological constituent for the therapy of the human HIV infectious disease containing the compound of a formula 1 or its salt which may be permitted in thrapeutics, and the support which may be permitted by the pharmaceutical-sciences target is contained within the limits of this invention. The range of this invention also includes the approach of treating a human HIV infectious disease including medicating Homo sapiens with the compound of the formula 1 of an effective dose, or its salt which may be permitted in thrapeutics. The approach of protecting the human cell which includes processing a human cell by the compound of the formula 1 of an anti-HIV effective dose or its salt which may be permitted in thrapeutics again from a HIV pathogen is included by the range. The manufacture approach of the compound of a formula 1 is explained below. The abbreviation generally used in this specification in order to display amino acid and a protective group is based on advice of the biochemistry naming IUPAC-IUB committee. "European Journal of Biochemistry" 138, 9 (1984) reference. For example, Val, Ile, and Asn And Leu The residue of L-valine, L-isoleucine, L-asparagine, and L-leucine is shown, respectively. The independent or branched chain-like alkyl group containing the straight chain-like alkyl group and the carbon atom of 3-4 with which the phrase "low-grade alkyl" used in this specification combining the radical of 1 contains the carbon atom of 1-6 is meant, and methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl and 1, and 1-dimethyl ethyl is included.

[0013] The independent or saturation cyclic hydrocarbon radical whose phrase "low-grade cycloalkyl" used in this specification combining the radical of 1 contains the carbon atom of 3-6 is meant, and cyclo propyl, cyclo butyl, cyclopentyl, and cyclohexyl are included. Phrase used in this specification "low-grade alkoxy one" The alkoxy group of the shape of a branched chain containing the straight chain-like alkoxy group and the carbon atom of 3-4 containing the carbon atom of 1-6 is meant, and methoxy and ethoxy ** propoxy, HEKISOKISHI, 1-methylethoxy, butoxy and 1, and 1-dimethylethoxy is included. The latter radical is tert. - It is usually known as butyloxy. The phrase "a halogen" used into this specification is a halogen radical chosen from a bromine, chlorine, a fluorine, and iodine. The phrase "Het" used into this specification is a univalent radical which hydrogen is removed and is obtained from the saturation or partial saturation

heterocycle of 5 containing the hetero atom of 1-2 which are chosen from nitrogen, oxygen, and sulfur, or 6 members. In arbitration, this heterocycle may have the substituent;, for example, low-grade alkyl, and low-grade alkoxy ** halogen, amino, or low-grade alkylamino of 1 or 2. The example of the heterocycle permuted by suitable heterocycle and arbitration includes pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1H-imidazole, 1-methyl-1H-imidazole, isoxazole, thiazole, 2-methyl thiazole, 2-aminothiazole, piperidine, 1, 4-dioxane, 4-morpholine, pyridine, 2-methylpyridine, pyrimidine, 4-methylpyrimidine and 2, and 4-dimethylpyrimidin. The phrase "residue" about amino acid means the radical obtained from the corresponding alpha-amino acid by removing the hydroxyl of a carboxy group, or the hydrogen of 1 of alpha-amino group.

[0014] The phrase "the support which may be permitted pharmacologically" used into this specification does not give an operation harmful to an active ingredient, but it is [for an active ingredient] nonpoisonous and, generally it means an inactive excipient. The phrase "an effective dose" used into this specification means the amount as which the compound of this invention effective enough was beforehand determined to HIV in in the living body. Generally, the reaction condition by which it is known that it is suitable for reagin is used for the compound of a formula 1, and it is manufactured by the learned approach. Edit according [the publication of an approach] to "Annual Reports In Organic Synthesis -1990" K. turn BAL, Academic Press, Incorporated, U.S. California San Diego, 1990 (and the above-mentioned "annual reports"), edit by "Vogel's Textbook of Practical Organic Chemistry" B.S. fur varnish, The long man group Limited, British Essex, 1986, and edit with "The peptides:Analysis, Synthesis, and Biology" E. glasses, A standard textbook like Academic Press, U.S. New York State New York, 1979-1987, and 1-9 volumes sees. When it explains especially, the compound of a formula 1 is the following process:(a) type 2 [0015].

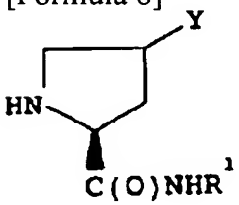
[Formula 7]



2

It is [the epoxide of (the inside of a formula and X are as the above-mentioned definition), and] a formula 3 [0016].

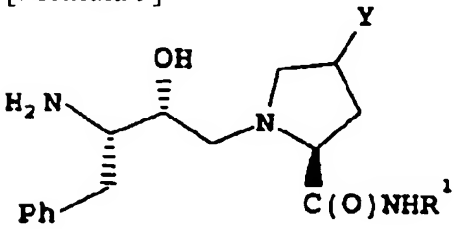
[Formula 8]



3

They are [whether the compound with which the pyrrolidine carboxamide of (the inside of a formula, R1, and Y are as the above-mentioned definition) is made to react, and a formula 1 (X, R1, and Y are as the above-mentioned definition among a formula, and B does not exist) corresponds is obtained, and]; or the (b) type 4 [0017].

[Formula 9]

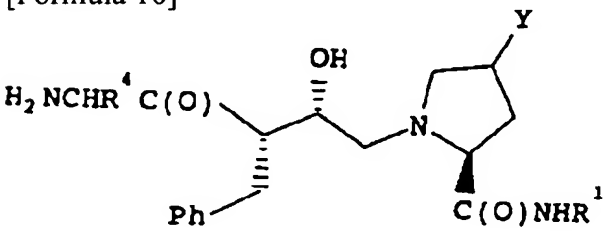


4

[0018] It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1,

and Y are as the above-mentioned definition). The reactant derivative of being R2 C (O) of the above-mentioned definition or R2AOCH2 C (O) is made to react. Formula 1 (X is R2 C [of the above-mentioned definition] (O), or R2AOCH2 C (O) among a formula) The corresponding compound with which R1 and Y are as the above-mentioned definition, and B does not exist is obtained, or they are; or the (c) type 4 (R1 and Y among a formula). The compound and formula X-NHCHR4 COOH (X and R4 among a formula) of being as the above-mentioned definition Coupling of the alpha-amino acid of being as the above-mentioned definition is carried out under existence of a coupling agent, and it is a formula 1 (X, R1, and Y among a formula). They are [whether it is as the above-mentioned definition and B obtains the corresponding compound of being divalent radical-NHCHR4 C(O)- (the inside of a formula and R4 being as the above-mentioned definition), and]; or the (d) type 5 [0019].

[Formula 10]



5

[0020] It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R4, and Y are as the above-mentioned definition). The reactant derivative of being R2 C (O) of the above-mentioned definition or R2AOCH2 C (O) is made to react, and it is a formula 1 (X). It is R2 C (O) or R2AOCH2 C (O), and is R1. And Y the passage of the above-mentioned definition -- it is -- B -- divalent radical-NHCHR4 C(O)- it is (the inside of a formula and R4 are as the above-mentioned definition) -- obtaining --; -- subsequently (e) It can be manufactured by changing the compound of the formula 1 obtained by the request in the above-mentioned section (a), (b), (c), or (d) into the corresponding acid addition salt which may be permitted in thrapeutics. The kind of the compound of a formula 1 (the inside X of a formula is N-protective group usually used, for example, Boc, Z, Fmoc, or p-methoxybenzyloxy carbonyl) is acquired most easily and conveniently by a process (a) and (C). Since it is easy to use this kind easily, it is useful as intermediate field for the suitable path which manufactures each compound of a formula 1 (the inside X of a formula is except N-protective group usually used) through each process (b) and (d). As intermediate field, therefore, the compound of this kind of formula 1 The amino terminal isolation amine which deprotection was carried out (that is, a protective group is removed), and was subsequently obtained A final manufacture of the compound of a formula 1 (the inside X of a formula is except N-protective group usually used, for example, 2-pilus JINIRU methoxycarbonyl, and 2-KINORI nil carbonyl) sake, According to a process (b) and (d), it is used by whether B exists or it exists as a compound of a formula 4 or a formula 5, respectively.

[0021] In order to make it clearer, according to the above-mentioned process (a), the compound of a formula 1 (B does not exist among a formula) can be manufactured by N-alkylation reaction including adding epoxide 2 to the pyrrolidine carboxamide 3. This reaction can be conveniently carried out in the temperature of 20-110 degrees C by putting in the two above-mentioned reacting matter in the state of contact into an inert solvent, for example, ethanol, a tetrahydrofuran, or dimethylformamide. Although reaction time is influenced by temperature and the property of reacting matter, the general range is 2 - 24 hours. According to a process (b), the compound of a formula 1 (B does not exist among a formula but X is R2 C [of the above-mentioned definition] (O), or R2AOCH2 C (O)) It is obtained, respectively by making the compound with which a formula 4 corresponds, and the reactant derivative of carboxylic-acid X-OH (the inside of a formula and X are R2 C (O) of the above-mentioned definition, or R2AOCH2 C (O), respectively) react. the acid halide which a suitable reactant derivative is the acylating agent which can offer suitable acyl group X-CO, and corresponds -- a chloride or a bromide, activity ester, an anhydride, or the mixed anhydride is included suitably. This reaction is performed according to the conditions for carrying out a reaction including a means to give desired selectivity to reacting matter choosing the learned approach and the suitable ratio of reacting matter, or by giving the protective group known by the request for the reaction radical besides either which competes with the reaction radical to mean temporarily. Generally, this reaction is performed the reaction time of the range of 15 minutes - 24 hours in the temperature of 0-50 degrees C in an inert solvent, for example, a tetrahydrofuran, dimethylformamide, or methylene dichloride.

[0022] According to the process (c), the compound of a formula 1 (the inside B of a formula is divalent radical-NHCHR4 C(O)- (the inside of a formula and R4 are as the above-mentioned definition)) can be obtained under existence of a coupling agent by carrying out coupling of the compound of a formula 4, and the alpha-amino acid of formula X-NHCHR4 COOH. Using a coupling agent and promoting dehydration coupling of the isolation carboxyl of the reacting matter of 1 and the isolation amino group of other reacting matter is;, for example, the volume ["The Peptides:Analysis, Synthesis, and Biology" / the 1st-8th volume] above-mentioned reference, known well. As an example of a suitable coupling agent, there are 1 and a - carbonyldiimidazole, or 1'N, N'-JISHIRORO hexyl-carbodiimide. As other examples, there is 1-hydroxy benzotriazol under existence of N and N-dicyclohexylcarbodiimide or an N-ethyl-N'-[(3-dimethylamino) propyl] carbodiimide. A very practical and useful coupling agent is its tris-(dimethylamino) phosphonium independently available (benzotriazol-1-yloxy) on the commercial target used under existence of 1-hydroxy benzotriazol. It is hexafluorophosphate. other very practical and useful coupling agents -- commercial -- available 2-(1H-benzotriazol-1-IRU)- N, N, and N'N'-tetramethyl URONIUMU It is tetrafluoroborate. A coupling reaction is performed in methylene dichloride, an acetonitrile, or an inert solvent like dimethylformamide. Diisopropyl ethylamine or a superfluous organic amine like N-methyl morpholine is added, and a reaction mixture is maintained to abbreviation pH 8. Reaction temperature is usually the range of -20 - 30 degrees C of abbreviation, and reaction time is 8 hours from for 15 minutes.

[0023] If a process (d) is referred to, this process will be performed by the same approach as the approach described above about the process (b), if it only removes using the compound of a formula 5 instead of the compound of a formula 4 as starting material. The epoxide of the formula 2 used as starting material in a process (a) can be manufactured by the approach which was learned or was learned. If it says in detail especially, the epoxide of a formula 2 can be manufactured by the approach which was indicated by the Europe patent application No. 346,847 by the B.K. pewters of December 20, 1989 issue, or was indicated by above-mentioned patent pending. The starting material of others in these processes, i.e., the pyrrolidine carboxamide of a formula 3, and the compound of formulas 4 and 5 are new, therefore are the object of this invention. The suitable approach for manufacture of the compound of formulas 4 and 5 was already explained above. The pyrrolidine carboxamide of a formula 3 can be manufactured by standard amidation of the known corresponding pyrrolidine carboxylic acid. J. "Chem.Soc.Perkins Trans." according [they] in alternative to F. sow C, D. well nick, and P. view RYU -- it can also manufacture by the approach of 1 and 2885 (1991). The manufacture approach of the pyrrolidine carboxamide of a formula 5 is explained in the following example.

[0024] The compound of the formula 1 of this invention can be obtained with the gestalt of the acid addition salt which may be permitted in thrapeutics. As an example of such a salt, a salt with a polymer acid, for example, a tannic acid, or a carboxymethyl cellulose and an inorganic acid, for example, halide acid, for example, a hydrochloric acid, a sulfuric acid, or a phosphoric acid is in an organic acid, for example, an acetic acid, a lactic acid, a succinic acid, a benzoic acid, a salicylic acid, methansulfonic acid or p-toluenesulfonic acid, and a list. It converts into the salt which may be permitted pharmacologically [other acid addition salts, for example, avirulent,] in a specific acid addition salt by processing with suitable ion exchange resin by "Helv.Chim.Acta" by R.A. BOISONASU and others, and the approach indicated by 43 and 1849 (1960) by request. Generally, the salt which may be permitted like thrapeutics of the peptide of a formula 1 is biologically [as the peptide itself] equal enough.

The cell protective effect over the HIV protease inhibition property and HIV pathogen of the compound of the biological viewpoint type 1 or its salt which may be permitted in thrapeutics can be proved by biochemical, microbiological, and the biological method. Especially the effective approach for proving the compound of a formula 1 or its HIV protease inhibition property of a salt which may be permitted in thrapeutics is "recombinant HIV protease HPLC assay." This approach is;H.G. clough SURIHHI et al. and the "Proc.Nat.Acad.Sci.USA." 86,807 (1989) reference based on the capacity for a trial compound to check enzyme division by the HIV protease of the deca peptide (substrate) which has an amino acid sequence including the HIV protease division part where HIV polyprotein was known. The result obtained with the instantiation compound of the detail about this assay and a formula 1 is indicated in the following example.

[0025] The capacity for the compound of a formula 1 and its salt which may be permitted in thrapeutics to protect a cell from HIV infection can be proved by the microbiological approach of evaluating the inhibition effectiveness of a trial compound over cytopathogenic [of HIV of Homo sapiens T-four cellular in]. Such an example of a type of an approach is indicated by "Science" by "Jpn.J.Cancer Res." (Gann) by S. Harada and N. Yamamoto, 76,543 (1985), and S. Harada and others, and 229 and 563 (1985). The assay based on the latter approach is indicated in the following example. When the compound of this invention or its salt

which may be permitted in thrapeutics is used in order to repulse a human HIV infectious disease, a medicine can be prescribed for the patient taking-orally-wise [this peptide] as an excipient containing 1 or the support beyond it which may be permitted pharmacologically, locally, or parenterally, and that rate is determined by the solubility, the chemical property, the selected route of administration, and standard biological custom of that compound. For internal use, said compound or its salt which may be permitted in thrapeutics can be prescribed by the capsule containing the active ingredient of the amount at which the range of about 5-150mg was beforehand appointed into the support which may be permitted pharmacologically, respectively, or unit administration gestalt object like a tablet. Said compound can be prescribed by the excipient which contains an activator 0.05 to 1% preferably 0.01 to 2% and which may be permitted pharmacologically for partial administration. these formula objects -- a cream, a lotion, and a sublingual tablet -- or it can consider as the gestalt of an endermic patch or a cheek patch preferably. For parenteral administration, the compound of a formula 1 is prescribed for the patient hypodermically or by carrying out an intramuscular injection in a vein as a constituent with the excipient or support which may be permitted pharmacologically. For administration by injection, it is desirable to use it in the solution in the sterilized water nature excipient which can also contain the solute of others like a buffer or a preservative enough besides the salt which may be permitted pharmacologically or glucose of an amount, in order to make a solution isosmotic for said compound.

[0026] The suitable excipient or the support for the above-mentioned formula object can be seen in a standard pharmaceutical-sciences textbook, for example, "Remington's Pharmaceutical Sciences", the 18th edition, a Mac publishing company, U.S. Pennsylvania Easton, and 1990. The dose of a compound changes with an administration gestalt object and the specific selected activators. Furthermore, it changes with the specific hosts under a therapy. Generally, a therapy is started by the small few dose more substantially than the optimal dose of a peptide. Then, it is increased by the dose by increasing little by little until the optimal effectiveness is acquired under the environment. Generally, as for this compound, it is most desirable to prescribe a medicine for the patient in the concentration criteria which generally acquire anti-viral effectiveness, without causing any harmful side effects harmful to ****** again. an internal use sake -- this compound or its salt which may be permitted in thrapeutics -- the weight per day of 1kg -- the range of 5-150mg -- a medicine is preferably prescribed for the patient in 5-50mg about the weight of 1kg. Although the compound of a formula 1 also has the above-mentioned variate in relation to generalized administration, it is 10micro per weight of 1kg g-1000microg. A medicine is prescribed for the patient with a dose. Although the formula object indicated above is the effective and comparatively safe physic for the therapy of a HIV infectious disease, such formula object and other anti-viral physic, or possible collaboration administration with ** is not eliminated. Such other anti-viral physic or ** includes fusibility CD 4, zidovudine, didanosine, zalcitabine, phosphono formate 3 sodium, RIBABARIN, aciclovir, or anti-viral interferon (for example, alpha-interferon or interleukin-2).

[0027]

[Example] Hereafter, an example explains this invention in more detail. Especially the percentage or ratio of a solution shows the relation of capacity pair capacity, unless it refuses. Temperature is shown by Centigrade. a proton nuclear-magnetic-resonance (NMR) spectrum -- Bruker 200MHz; recorded on the spectrometer -- a chemical deviation (delta) -- ppm It is reported. The abbreviation used into the example Boc : tert - Butyloxy carbonyl; [BOP] : benzotriazol-1-yloxy tris(dimethylamino)phosphonium hexafluorophosphate; -- But : tert- butyl; -- Bzl : benzyl; -- DIEA:diisopropyl ethylamine; -- DMF : dimethylformamide; -- HEPES : N-2-hydroxyethyl piperazine-N'-2-ethane-sulfonic-acid; -- Et2O:diethylether; -- EtOAc : ethyl-acetate;EtOH: -- ethanol;HPLC: -- high-performance-liquid-chromatography;MeOH: -- methanol ;P h:phenyl; -- THF : Tetrahydrofuran;Z : include benzyloxycarbonyl.

[0028] Example 14(S)-benzyloxy-N-manufacture N of the tert-butyl-1-(tert-butyloxy carbonyl) pyrrolidine-2(S)-carboxamide (a) - The protected acid, 1-(tert-butyloxy carbonyl)- a 4(S)-hydroxy pyrrolidine-2(S)-carboxylic acid under existence of NaOH superfluous in a THF/H2 O (1:1) solution In a room temperature 18 hours, 4(S)-hydroxy pyrrolidine-2(S)-carboxylic-acid {cis--4-hydroxy-L-proline, S. It manufactured by making written} and G tert-butyl cull BONETO react to G. Lamaism SUWAMI and "J.Org.Chem." by E. Adams, and 42 and 3440 (1977). (b) N obtained by doing in this way - The protected acid (400mg, 1.73mmol) was dissolved into DMF (7ml). Sodium hydride (99%, 87mg, 3.63mmol) was added in this solution. The obtained mixture was agitated in the room temperature (20-22 degrees C) for 2 hours. The benzyl bromide (1.03ml, 8.65mmol) was added, and the obtained mixture was agitated in the room temperature for 18 hours. Then, it is EtOAc about this mixture. It diluted, it cooled at 0 degree C, and considered as acidity (pH3) by adding an aquosity citric acid 10%. The organic layer was separated, H2 O

and brine washed, it dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. A chromatography (SiO2, an eluate: hexane-EtOAc, 9:1) refines the yellow oily matter which remained, and it is 4 (S). - Benzyloxy-1-(tert-butyloxy carbonyl) pyrrolidine-2(S)-carboxylic-acid benzyl ester (301mg, 70%) was obtained.

[0029] (C) The latter compound (301mg, 0.73mmol) was dissolved into MeOH/H2O (2:1 or 4ml). The obtained solution was agitated and it cooled at 0 degree C. Aquosity 2M solution (1.16ml) of NaOH was added. After 10 minutes, this mixture was warmed to the room temperature and it agitated in the same temperature for 18 hours. Then, it is reagin Et2O/It diluted by the hexane (1:1 or 10ml) and H2O (5ml). An aquosity layer is separated and it is Et2O/. The hexane (1:1) extracted twice, it cooled at 0 degree C, and considered as acidity by the aquosity citric acid 10% (pH3), and EtOAc (3X) extracted. Doubled EtOAc H2O and (2X) brine washed the extract, and it dried (MgSO4) and condensed under reduced pressure. Survival is dried under a high vacuum and it is 4(S)-benzyloxy [of quantitative yield]. - 1 -(tert-butyloxy carbonyl)- The pyrrolidine-2(S)-carboxylic acid was obtained. (d) CH2 Cl2 DIEA (127 mul, 0.73mmol) is added in the solution of 0.2 M of the compound (234.7mg, 0.73mmol) of the inner latter, and, subsequently it is tert. - A butylamine (84.4microl and 0.803mmol) and BOP (387mg and 0.876mmol) were added. It agitated in the room temperature for 3 hours, maintaining that pH to 8 by reaching this reaction mixture by periodic inspection, and adding DIEA if needed. Then, it is EtOAc about a reaction mixture. It dilutes and they are the saturated water solution (2X) of NaHCO3, and H2O. And brine washed continuously. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 7:3 after that 6:4) refined the oily matter of the obtained yellow, and the mark compound was obtained (252mg, 92%). 1NMR(CDCl3) delta7.40-7.25 (m, 5H), 6.05 (double width s, 1H), and 4.6 -4.35 (double width d, 2H), 4.2-4.05 (m, 2H), and 3.8-3.55 (m, 2H) 2.55-2.1 (m, 2H) -- 1.46 (s, 9H) and 1.20 (double width s, 9H).

[0030] example 21- {3(S)-amino-2(R)-hydroxy-4-phenyl butyl} -4 (S) -- the - benzyloxy-N-tert-butyl pyrrolidine-2(S)-carboxamide () [formula 4:R1 =C 3 (CH3) and] [Y=OCH2 Ph;C] (O) The solution of the mark compound (250mg and 0.664mmol) of the formula 1 in NHR1 / Y= cis- (Manufacture a) 6NHCl / dioxane was agitated for 20 minutes in the room temperature, and, subsequently concentration hardening by drying was carried out under reduced pressure. Survival was diluted by EtOAc and (10ml) the 2-N aquosity NaOH (3ml). The obtained mixture was agitated for 15 minutes in the room temperature. An organic layer is separated and it is H2O of the minimal dose. And brine washed, it dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. survival -- the bottom of a high vacuum -- drying -- 4 (S) -- the - benzyloxy-N-tert-butyl pyrrolidine-2(S)-carboxamide and the carboxamide of a formula 3 (the inside of a formula and R1 -- C 3 (CH3) and Y -- OCH2 -- it is Ph {C (O) NHR1 / Y= cis-}) were obtained. (b) The latter compound was mixed with 3(S)-(benzyloxycarbonyl)-1 and 2(R)-epoxy-4-phenyl butane (180mg, 0.604mmol) 2 (the inside of a formula and X are Z), i.e., a formula, in anhydrous [EtOH] (5ml). Refer to [above-mentioned / B.K. pewter]. This mixture was heated under reflux for 18 hours, and, subsequently concentration hardening by drying was carried out under reduced pressure. survival -- flash chromatography (SiO2, eluate:CHCl3-MeOH, 39:1 after that 19:1) -- refining -- four -- (-- S --) - benzyloxy one - one - {-- three -- (-- S --) - {(benzyloxycarbonyl) -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide (220mg, 63%) -- as a white foamy object -- having obtained .

(c) The latter compound (220mg and 0.384mmol) was given to hydrogenolysis (5%M, Pd/C, H21 atmospheric pressure, MeOH, and 3.5 time amount), the compound of a mark was obtained, and it used according to coupling actuation of the following example immediately.

[0031] an example -- 34 -- (-- S --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide (formula 1: B=Val [X=Z and]) R1 =C 3 (CH3) And Y=OCH2 Ph;C (O) NHR1/Y = a cis- manufacture mark compound :DIEA (33.4microl --) manufactured according to the following coupling approach 0.192mmol(s), protected amino acid Z-Val-OH (53.1mg, 0.211mmol), and BOP (102mg, 0.23mmol) were added in 0.2 M solution (0.192mmol) of the mark compound of the example 2 in CH2Cl2. It maintained to pH8 by adding DIEA periodic inspection and if needed, agitating this reaction mixture in a room temperature for 2 hours. Then, it is EtOAc about this reaction mixture. It dilutes and they are the saturated water solution (2X) of NaHCO3, and H2O. And brine washed continuously. The organic layer was dried (MgSO4) and it condensed under reduced pressure. Flash chromatography (SiO2, eluate:CHCl3-MeOH, 39:1) refined survival, and the mark compound of this example was obtained as a white solid (108mg, 83%). A FAB mass spectrum and m/z:673.3(M+H)+.

[0032] an example -- 44 -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide (formula 1: B=Val [X=Z and]) R1 =C 3 (CH3) And Y=OCH2 Ph;C In the section (a) of the manufacture example 1 of (O) NHR1 / Y= transformer instead of a 4(S)-hydroxy pyrrolidine-2(S)-carboxylic acid Except using "an equivalent 4(R)-hydroxy pyrrolidine-2(S)-carboxylic acid (transformer-4-hydroxyproline-2-carboxylic acid), above-mentioned S.G. Lamaism SUWAMI, and refer to E. Adams", the procedure of examples 1, 2, and 3 was followed continuously, and the mark compound was obtained. A FAB mass spectrum and m/z:673.3+ (M+H).
[0033] an example -- 54 -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide (formula 1: B=Asn [X=Z and]) R1 =C 3 (CH3) And Y=OCH2 Ph;C In the section (a) of the manufacture example 1 of (O) NHR1 / Y= transformer instead of a 4(S)-hydroxy pyrrolidine-2(S)-carboxylic acid Except using an equivalent 4(R)-hydroxy pyrrolidine-2(S)-carboxylic acid The procedure of examples 1 and 2 is followed continuously. and 1- obtained by doing in this way -- {3(S)-amino-2(R)-hydroxy-4-phenyl butyl} -4 (R) -- the - benzyloxy-N-tert-butyl pyrrolidine-2(S)-carboxamide was given to the following coupling process, and the mark compound was obtained.
[0034] 1-hydroxy benzotriazol (20.1mg, 0.148mmol) was added to the solution (0 degree C) with which N in THF (2ml) and N'-dicyclohexylcarbodiimide (34mg, 0.165mmol) were cooled. This mixture was agitated for 15 minutes. 1- described above in the solution of amino acid Z-Asn-OH (395mg, 0.148mmol) from which it was protected in DMF (1ml), and DMF (1ml) -- {-- 3 (S) - amino-2(R)-hydroxy-4-phenyl butyl --} -4 (R) -- the - benzyloxy-N-tert-butyl pyrrolidine-2(S)-carboxamide (35.4mg, 0.083mmol) was added to this mixture. To the room temperature, the obtained mixture was warmed slowly and, subsequently was agitated for 18 hours. Then, it is EtOAc about this mixture. It diluted. An organic layer is separated and they are the saturated water solution of NaHCO3, and H2O. And brine washed, it dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, eluate:EtOAc/MeOH, 97:3 after that 19:1) refined white solid survival, and the mark compound of this example was obtained. EI mass spectrum and m/e:389.2+ (M+2H). (Notice the coupling approach illustrated to the above which uses 1-hydroxy benzotriazol under existence of N and N'-dicyclohexylcarbodiimide about the suitable coupling approach for manufacture of the compound of a formula 1 (amino acid residue Asn is shown by the inside B of a formula) being shown.)
[0035] example 64(S)-benzyloxy-1 - {3(S)-{{N-(benzyloxycarbonyl) asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl --} -- the -N-tert-butyl pyrrolidine-2(S)-carboxamide (formula 1: B=Asn [X=Z and]) R1 =C 3 (CH3) And Y=OCH2 Ph;C (O) NHR1/Y = the procedure of the cis- manufacture examples 1 and 2 and the coupling approach of an example 5 were followed continuously, and the mark compound was obtained. A FAB mass spectrum, m/z:688.4+ (M+H) ; 710.4(M+Na)+.
X=Z an example -- 71 - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -4(S)-(2-methylpropyl oxy-) pyrrolidine-2(S)-carboxamide {type 1: -- B=Val and R1 =C 3 (CH3) And Y=OCH2CH2 (CH3) ; C In the procedure of the section (b) of the manufacture example 1 of (O) NHR1 / Y= cis-} Except using 2-methylpropyl bromide of the equivalent instead of a benzyl bromide, the procedure of examples 1, 2, and 3 was followed continuously, and the mark compound was obtained. EI mass spectrum and m/e:583.4+ (MH2-C4H9).
[0036] X=Z an example -- 81 - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N - tert - butyl -4(R)-(2-methyl propoxy) pyrrolidine-2(S)-carboxamide {type 1: -- B=Val, R1 =C 3 (CH3) And Y=OCH2CH2 (CH3) ; C In the procedure of the section (a) of the manufacture example 1 of (O) NHR1 / Y= transformer} An equivalent 4 (R)-hydroxy pyrrolidine-2(S)-carboxylic acid is used instead of a 4(S)-hydroxy pyrrolidine-2(S)-carboxylic acid. Except using equivalent 2-methylpropyl bromide instead of a benzyl bromide in the section (b) of an example 1, the procedure of examples 1, 2, and 3 was followed continuously, and the mark compound was obtained. EI mass spectrum and m/e:583.3+ (MH2-C4H9).
[0037] an example -- 94 -- (-- R --) - benzyloxy ones - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N - cyclo -- propyl -- a pyrrolidine - two -- (-- S --) - the carboxamide (formula 1: B=Val [X=Z and]) R1 = cyclo propyl and Y=OCH2 Ph;C In the section (a) of the manufacture example 1 of (O) NHR1 / Y= transformer The 4(R)-hydroxy pyrrolidine-2(S)-carboxylic acid of the equivalence instead of a 4(S)-hydroxy

pyrrolidine-2(S)-carboxylic acid, Except using the cyclo PIROPIRU amine of the equivalent instead of a tert-butylamine in the section (d) of an example 1, the procedure of examples 1, 2, and 3 was followed continuously, and the mark compound was obtained. EI mass spectrum and m/e:657.5+ (M+H).
an example -- 104 - benzyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N-tert - butyl -- a pyrrolidine - two - - (-- S --) - the carboxamide (formula 1: B=Asn [X=Z and]) R1 =C 3 (CH3) And manufacture of 4 (R, S), 4 (R), and 4 (S) isomers of Y=Bzl [0038] The approach indicated by above-mentioned F. sow C, D. well nick, and P. view RYU was applied, and the mixture (3:2, w/w) of 4 (R) and 4 (S) diastereomers of a 4-benzyl-1-(tert-butyloxy carbonyl) pyrrolidine-2(S)-carboxylic acid was obtained from serine lactone and 3-phenyl-2-propenyl bromide. BOP By coupling by the approach of the section (d) of the example 1 of the diastereomer mixture under existence, and a tert-butylamine, the diastereomer mixture with which 4 (R) of the N-tert-butyl-1-(tert-butyloxy-carbonyl) pyrrolidine-2(S)-carboxamide and 4-benzyl-4 (S) isomer correspond was obtained. then -- an example -- two -- a section -- (-- b --) -- a procedure -- and -- a formula -- three -- the carboxamide -- ****** -- the latter -- a diastereomer -- mixture -- using it -- things -- four - benzyl - one - {- - three -- (-- S --) - {(benzyloxycarbonyl) - amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl - -} - N-tert - butyl -- a pyrrolidine - two -- (-- S --) - the carboxamide -- four -- (-- R --) -- and -- four -- (-- S - -) -- an isomer -- corresponding -- a diastereomer -- mixture -- having obtained . A FAB mass spectrum and m/z:558+ (M+H). moreover, the reaction by the coupling approach of the example 5 with amino acid Z-Asn-OH of which N-protection was done with the mixture of the latter diastereomer -- the 4-benzyl -1 - {3 (S)-{{N-(benzyloxycarbonyl) asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl --} -- the diastereomer mixture with which 4R of the -N-tert-butyl pyrrolidine-2(S)-carboxamide and 4S isomer correspond was obtained. A FAB mass spectrum and m/z:672+ (M+H).
[0039] The HPLC technique separated these two isomers and pure corresponding 4R and 4S corresponding isomer were obtained. If it explains in detail, it is 2.5ml (the first condition) of 50% aquosity acetic acids. It was filled up with the 20ml sample of the mixture indicated at the last dissolved in inside on Watt Mann Magnum 9 (trademark) and C18 octadecyl silyl column (0.94x50cm). An early column equilibrium condition is :10%A and 90%B (0.06% trifluoroacetic acid in a pump A:acetonitrile; pump B:H2O inside 0.06% trifluoroacetic acid) which are as follows. once it passes the peak (transverse plane of a solvent) corresponding to an acetic acid -- a line -- inclination continued. The separation program of an isomer is a part for 30 - 100%A for [110 minutes] and 3ml/, and 230nm between the :10 - 30%A5 part which was as follows, for [30%A] 10 minutes, and after that. 4 (R) isomers and 4 (S) isomers were collected in 60%A (9.2mg) and 63%A (8.3mg), respectively.
[0040] Example 11 N-tert-butyl-1-{2 (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - two - quinolyl -- carbonyl -- the valyl --} -- amino --} - butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide (B=Val formula 1;X=2-quinolyl carbonyl --) R1 =C 3 (CH3) And manufacture N of Y=2-pyrimidinyl thio (a) - The protected acid (it indicates into the section (a) of 17.5g, 75.6mmol, and an example 1) was dissolved into CH2Cl2 (300ml) and DIEA (13ml, 76.6mmol). The tert-butylamine (8.73ml, 83.1mmol) was added in this solution, and, subsequently BOP and (40g, 90.7mmol) DIEA (13ml, 151mmol) were added. This mixture is agitated in a room temperature for 7 hours, and, subsequently it is EtOAc. It diluted. The organic layer was separated, the saturated water solution (2X) of NaHCO3, H2O, and (2X) brine (2X) washed, and evaporation to dryness was dried and (MgSO4) carried out. the obtained solid survival -- Et2 O/EtOAc (9:1) -- grinding -- a filter paper top -- collecting -- Et2O -- washing -- drying -- N-tert-butyl-1-(tert-butyloxy carbonyl)- the 4(R)-hydroxy pyrrolidine-2(S)-carboxamide (15.6g, 72%) was obtained.
[0041] (b) The latter compound (5.0g, 17.5mmol) was dissolved into toluene/THF (3:1 or 175ml). Triphenyl phosphine (5.72g, 21.8mmol) and an imidazole (1.08g, 30.5mmol) were added in the solution in the room temperature. The obtained mixture was warmed at 45-50 degrees C. Iodine (5.54g, 21.8mmol) was added and the obtained mixture was violently agitated in 45-50 degrees C for 80 minutes. Then, this reaction mixture is cooled and they are Et2O and H2O. It diluted. The organic layer was separated, the saturated water solution (1X) and brine (1X) of NaHCO3 washed, it dried, and evaporation to dryness (MgSO4) was carried out, and the oily matter of the brown containing some solids (oxidation triphenyl phosphine) was obtained. This oily solid was ground by Et2O, and solids were collected on the filter paper. Evaporation to dryness of the filtrate was carried out, and brown oily matter was obtained. this oily matter -- flash chromatography (SiO2, eluate:EtOAc / hexane, 1:4) -- refining -- N-tert-butyl-1-(tert-butyloxy carbonyl)-the 4(S)-iodine pyrrolidine-2(S)-carboxamide was obtained as a yellow solid (4.83g, 70%). 1NMR(CDCl3) delta6.2-6.0 (double width s, 1H), 4.27-4.0 (m, 3H), 3.75-3.55 (m, 1H), 2.9-2.5 (m, 2H), 1.47 (s, 9H), 1.38

(s, 9H).

[0042] (c) It added one drop of 2-pyrimidine thiol (1.06g, 9.46mmol) at a time to the suspension (0 degree C) by which the sodium hydride (99%, 182mg, 7.57mmol) in DMF (10ml) was cooled. This mixture was agitated for 30 minutes at the same temperature. Then, it added one drop of solution of the product (1.5g, 3.79mmol) of the above-mentioned section (b) in DMF (5ml) at a time to this mixture. This reaction mixture is agitated in a room temperature for 18 hours, and, subsequently it is EtOAc. And H2O It diluted. The organic layer was separated, 1-N aquosity solution (2X) and brine (1X) of cold H2O (1X) and NaOH washed, it dried, and (MgSO4) evaporation to dryness was carried out, and the solid was obtained. the place which ground this solid by Et2O -- N-tert-butyl-1-(tert-butyloxy carbonyl)- the 4(R)-(2-pyrimidinyl thio) pyrrolidine-2(S)-carboxamide was obtained as a solid of an off-white. 1NMR(CDCl3) delta8.53-8.51 (d -- J= 4.85Hz) 2H and 7.01-6.96 (t and J= -- 4.85 or 10.0Hz) 1.47 (s, 9H) 1H, 5.97-5.75 (double width s, 1H), 4.4-4.2 (m, 2H), 4.1-3.91 (m, 1H), 3.70-3.35 (m, 2H), 2.92-2.75 (m, 1H), 1.36 (s, 9H). FAB mass spectrum (m/z): 381(M+H)+ and 403+ (M+Na).

(d) Carry out deprotection of the latter compound and follow the section (a) of an example 2, and the approach of (b). It is made to react with the epoxide of a formula 2 (the inside of a formula and X are Boc (s)). N - tert - butyl - one - {-- three -- (-- S --) - {(tert-butyloxy carbonyl) -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide -- having obtained . A FAB mass spectrum, m/z:544(M+H)+, and 566(M+Na)+. or -- the latter -- a compound -- an example -- two -- a section -- (-- a --) -- a procedure -- following -- deprotection -- carrying out -- an example -- three -- a procedure -- following -- Boc-Val-OH -- coupling -- carrying out -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (tert-butyloxy carbonyl) -- the valyl --} - - amino --} - two -- (-- R --) - hydroxy one - -- four -- - phenyl -- butyl --} - four -- (-- R --) - 2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide -- having obtained -- . FAB mass spectrum (m/z): 643(M+H)+ and 665(M+Na)+.

[0043] (e) The solution of the compound (887mg, 1.38mmol) of the latter in HCl/dioxane of 6 N (7ml) was agitated for 20 minutes in the room temperature. This solvent was removed under reduced pressure. The survival of a white solid was dried for 20 minutes under the high vacuum, and the corresponding amine by which deprotection was carried out was obtained as a hydrochloride. The latter salt was dissolved into CH2Cl2 (7ml) and DIEA (481 mul, 2.76mmol). 2-quinoline carboxylic acid (263ml, 1.52mmol) and BOP (732mg, 1.66mmol) were added in the solution of this salt. pH of this reaction mixture was agitated in the room temperature for 5 hours, maintaining to 8 by adding a periodic inspection and periodic DIEA as occasion demands. Then, it is EtOAc about this reaction mixture. It diluted and the saturated water solution (2X) of NaHCO3, H2O (2X), and brine washed continuously. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 3:7, and after that 1:9) refined the obtained colorless oily matter, and the mark compound was obtained as a white foamy object (750mg, 78%). When this foamy object was ground by Et2O, the mark compound was obtained as a white solid (378mg, 40%). A FAB mass spectrum, m/z:698 (M+H)+, and 720(M+Na)+. NMR of this compound was the same as the specified structure. Except using 3-pyridine methanethiol instead of 2-pyrimidine thiol in a section (c) The procedure of this example is followed. N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} - amino --} -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a pyrrolidine - two -- (-- S --) - the carboxamide -- obtaining . A FAB mass spectrum, m/z:711(M+H)+, and 733(M+Na)+. It sets into a section (c) again. Instead of 2-pyrimidine thiol The procedure of this example is followed except using a 2 and 6-dimethyl-4-hydroxy pyrimidine. N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2, 6-dimethyl-4-pyrimidinyl) -- oxy-one --} -- a pyrrolidine - two -- (-- S --) - the carboxamide -- obtaining . A FAB mass spectrum, m/z:710 (M+H), and 586(M+H-C6H8N2O)+.

[0044] Example 12 N-tert-butyl-1-{3 (-- S --) - {-- {(2, 6-dimethyl phenoxy) -- acetyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide (formula 1;X= (2, 6-dimethyl-phenoxy) acetyl --) B does not exist but is R1 =C 3 (CH3). And indicated the section (d) of the manufacture example 11 of Y=2-pyrimidinyl thio. N-tert - butyl - one - {-- three -- (-- S --) - {-- N - (tert-butyloxy carbonyl) -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a pyrrolidine - two -- (-- S --) - the carboxamide -- It is Boc by the usual approach. By removing a protective group, the corresponding primary amine, That is, it converted into the N-tert-butyl-1-(3 (S) - amino-2(R)-hydroxy-4-phenyl butyl)-4

(R)-(2-pyrimidinyl thio) pyrrolidine-2-carboxamide. According to the procedure of an example 3, coupling of the latter compound was carried out to the acetic acid (2, 6-dimethyl phenoxy), and the mark compound was obtained. A FAB mass spectrum, m/z:606(M+H)+, and 628(M+Na)+.

[0045] A primary amine [/ instead of said primary amine], N-tert-butyl-1- () [3] (S) - amino -2 (R) - hydroxy-4-phenyl butyl -4 (R) - {-- the (3-pilus JINIRU methyl)-thio} pyrrolidine-2-carboxamide (an example -- 11 -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} - butyl --} - four --) (R) -- it is used as intermediate field of the - {(3-pilus JINIRU methyl) thio} pyrrolidine-2(S)-carboxamide -- having had -- except using it this example -- a procedure -- following -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- two -- six - dimethyl -- phenoxy -- acetyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - {(3-pyrimidinyl methyl) - thio --} -- a pyrrolidine - two -- (-- S --) - the carboxamide -- A FAB mass spectrum, m/z:619(M+H)+, and 641+ (M+Na) It obtained.

[0046] example 13 recombination HIV protease assay: -- enzyme: -- {structure pBRT1prt+, W.G. Farr Mary et al., "Science", 236, and 305 (1987) reference}: which expressed the HIV protease in E.coli according to the following procedure -- all solutions are aquosity solutions unless it refuses especially.

(i) -- fermentation pBRT1prt+ Luria-BERUTA which uses the E.coli cell containing a plasmid and contains the ampicillin of 100microg / ml -- nib -- it ****(ed) to the inoculation culture medium which consists of a loss. It incubated in 37 degrees C, moving a flask violently for 17 hours. In the generation flask to which the ampicillin of 100microg / ml was supplied including sterilization M9 broth, it ****(ed) by 1% (v/v) of concentration using the above-mentioned inoculation culture. The full capacity in each generation flask was 500ml among the Erlenmeyer flask of 2L. Optical density 0.6 (lambda= 540nm) In 37 degrees C, it incubated, moving a flask violently until it became corresponding cell concentration (with no dilution). The range of this time amount is usually 3 - 4 hours. Subsequently, 5mM isopropyl thiogalactoside (IPTG, research auger NIKUSU, U.S. Ohio Cleveland) is supplied to a flask, and it sets to the dilution it is 16 times whose cell concentration of this, and is optical density 0.2. Incubation was continued until it became. subsequently, a flask -- 1mM phenylmethyl sulfonyl fluoride (PMSF) -- supplying -- base -- it refrigerated at 4 degrees C quickly. The centrifugal separation in 4 degrees C recovered this bacterial cell. The obtained humid pellet was saved in -70 degrees C.

[0047] (ii) The extract of the enzyme of an assay grade and especially all the processes of the manufacture following were performed in 4 degrees C, unless it refused. the frozen cell -- the buffer solution A -- {-- 50mM tris (hydroxymethyl) aminoethane HCl(tris - HCl, pH7.4);0.6mM ethylenediaminetetraacetic acid (EDTA); -- to 0.375 MNaCl, 0.2 %NonidetP-40(trademark) (BDH KEMIKARUZU Limited, British pool);1mMPMSF}, and the cell weight 1 section, the buffer-solution A9 section came out comparatively, and it added. ** sow soil (cerite 545 (trademark), a JON man building, a ROM pock, U.S. California) was added at a rate of the two sections to the humid cell weight 1 section. The obtained slurry was homogenized at high speed (about 20,000 rpm) on the wearing (trademark) industrial use blender by the pulse for 8x 15 seconds. It is the pellet which collected the fragment/cerite of a cell (trademark) according to centrifugal separation, and was obtained to the humid solid 1 section Buffer-solution A4.5 It extracted by the above-mentioned homogenization approach using the section. The supernatant liquid obtained from both the homogenization process was doubled, fusibility protein was settled by adding solid (NH4) 2SO4, and 75% saturation of the last concentration was obtained. This mixture was violently moved for 60 minutes, and centrifugal separation recovered precipitate. the obtained pellet -- buffer-solution B{50mM tris-HCl and pH8;30mMNaCl; 1mMDL-dithiothreitol (DTT); -- 1mMEDTA;1mMPMSF;10% glycerol} -- it suspended in inside and dialyzed to the same buffer solution for 18 hours.

[0048] It was filled up with the aliquot of the dialyzed extract containing 150mg of protein on the sephadex A25 (trademark) anion exchange column (Pharmacia, salary the Sweden country rise) which has the floor dimension of 70cm length, and the path of 2.5 cm. a sample -- a line -- in the 10cm [/hour] rate of flow, it eluted in isocratic one with the buffer solution B. The fraction (see the publication about the following assay) including HIV protease activity was doubled, the protein of fusibility was precipitated by adding saturated water nature (NH4) 2SO4, and 85% saturation of ** (NH4) 2SO4 concentration was obtained. They are buffer-solution C{50mM2-(4-morpholino) ethane sulfonic acid (MES) and pH5.5 about the pellet which removed precipitating protein according to centrifugal separation, and was obtained.;150mMNaCl;1mMDTT;1mMEDTA;10% glycerol} It dissolved in inside. This precipitate was dialyzed to the buffer solution C for 18 hours, and, subsequently it froze in -70 degrees C. By the same approach as the approach of the above-mentioned publication of all crude extracts, it was made the aliquot containing 150mg of protein, and the chromatography refined. The last manufactures obtained from each

batch are collected, and it is 34microL. It divided into the aliquot and saved in -70 degrees C. The divided substrate / part / mg had the specific activity of the HIV protease of 18.2mmol(s), and the last protein collected from the fermentation of 20L was 300mg typically. Before use, the aliquot was diluted to 1/38 of the first concentration with the buffer solution (refer to following) (namely, enzyme operation solution).
Substrate: VSFNFPQITL-NH2 and MW1164 (clough SURIHHI et al., "Proc.Natl.Acad.Sci.USA" 86,807 (1989) reference) were used as a substrate. This substrate was set to stock 10mM in DMSO, and was saved at 4 degrees C. Before use, this stock was diluted with the buffer solution and 400micro of solutions M was obtained (namely, substrate operation solution).
[0049] Buffer solution: It is the solution which dissolved MES (100mM), KCl (300mM), and EDTA (5mM) into distillation H2O (90ml), and was obtained by the dark aquosity NaOH 5.5 It adjusted. It is H2O about the latter solution. It diluted, and was referred to as 100ml, and the buffer solution was obtained.
Procedure: (1) assay mixture is substrate operation solution 20microl and solution 10microl of the trial compound in 10%DMSO. And enzyme operation solution 10microl It manufactured by mixing. (2) This assay mixture was incubated for 30 minutes in 37 degrees C. (3) About reagin, it is 2% aquosity trifluoroacetic acid 200microl. It quenched by adding. (4) Assay mixture 100microl which it quenched ****** given to HPLC which uses Perkin-Elmer 3x3CRC8 column (no [PerkinElmer, Incorporated and U.S. Connecticut] work piece) by the gradual inclination in a part for 4ml/of the rates of flow separated the substrate and the product (namely, VSFNF and PQITL-NH2). The following passes, it comes out and this inclination is certain :0.0-0.5. 70%A/part and 30%B;
0.5-3.0 67%A/Part and 33%B;
3.0-5.0 20%A/Part and 80%B;
5.0-6.5 70%A/Part and 30%B;
(Above A is H2O It is inner 3mM sodium dodecyl sulfate / 0.05%H3PO4, and B is 0.05%H3PO4 among an acetonitrile) . Elution was supervised in 210nm. (5) The contrast which is assay mixture without a trial compound was given to processes 2-4 at coincidence.
[0050] Consideration of inhibition: The quantum of a division product and the parent substrate of survival was carried out according to the integral of the height of a peak, or a suitable HPLC peak. The enzyme inhibition of the :inversion (%) =(peak height [of the sum total / substrate of the peak height of a product or a peak area, and a product] or sum total of peak area) x100 trial compound which computed substrate inversion using the following relational expression was computed as follows.
The concentration 50 of the trial compound which brings about 50% inhibition of an inhibition (%) =100-(inversion of inversion (%) / contrast of assay mixture (%)) x100HIV-protease, i.e., IC, measured the inhibition percentage of :enzyme measured as follows about the min of three different concentration of a trial compound. Then, it determined on the graph by plotting the inhibition percentage of an enzyme [as opposed to the concentration of a trial compound for IC50]. IC50 of the instantiation compound of a formula 1 measured in recombination HIV protease HPLC assay is hung up over following front Naka.
[0051]
[Table 1]
A Table 1 number A compound IC50 (nM) 1 4 (S) - Benzyloxy-1-{3(S)-{{N- 150 Valyl} amino}-(Benzyloxycarbonyl) 2(R)-hydroxy-4-phenyl butyl}-N- The tert-butyl-pyrrolidine-2(S)-carboxamide 2 4 (R) - Benzyloxy-1-{3(S)-{{N- 16 (benzyloxycarbonyl) Valyl} amino}-2(R)-hydroxy-4-phenyl butyl}-N- The tert-butyl pyrrolidine-2(S)-carboxamide ---------- 3 4 (R) - Benzyloxy-1-{3(S)-{{N- 39 Asparaginyl}- (Benzyloxycarbonyl) Amino}-2(R)-hydroxy-4-phenyl - Butyl}-N-tert-butyl-pyrrolidine - 2 (S)-carboxamide 4 4(S)-benzyloxy-1-{3(S)-{{N- 300 Asparaginyl} amino}- (Benzyloxycarbonyl) 2(R)-hydroxy-4-phenyl butyl}-N- The tert-butyl-pyrrolidine-2(S)-carboxamide 5 1-{3(S)-{{N-(benzyloxycarbonyl)- 745 Valyl} amino}-2(R)-hydroxy-4- Phenyl butyl}-N-tert-butyl -4 (S) - Pyrrolidine -2 (S) - (2-methylpropyl oxy-) The carboxamide six -- -- one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - -- 180 -- -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl - - - butyl --} - N-tert - butyl - four -- (-- R --) - () [2-methyl-] The propyloxy pyrrolidine-2(S)-carboxamide 7 four -- (-- R --) - benzyloxy one - one - {-- three -- (-- S --) - {-- {-- N - 100 -- (benzyloxycarbonyl) -- the valyl --} -- amino --} - -- two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - N - The cyclo propyl pyrrolidine-2(S)-carboxamide 8 4 (R) - Benzyl-1-{3(S)-{{N- 48 Asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl}-N- (Benzyloxycarbonyl) The tert-butyl-pyrrolidine-2(S)-carboxamide 9 4 (S) - Benzyl-1-{3 (S)-{{N- 780 Asparaginyl} amino}- (Benzyloxycarbonyl) 2(R)-hydroxy-4-phenyl butyl}-N- tert-butyl-pyrrolidine-2(S)-carboxamide 10 N-tert - Butyl-1-{2(R)-hydroxy-4- 4.7 Phenyl-3(S)-{{N - () [2-kino RINIRU-] Carbonyl valyl} amino} butyl}-4(R)- (2-pyrimidinyl thio)-pyrrolidine -2 (S) - Carboxamide 11

N-tert - Butyl-1-{2(R)-hydroxy-4- 12 phenyl - three -- (-- S --) - {-- {-- N - (2-kino RINIRU - carbonyl) -- the valyl --} -- amino --} -- butyl --} -4 (R) - {(3-pilus JINIRU methyl) - thio} pyrrolidine - 2(S)-carboxamide 12 N-tert-butyl-1-{2(R)-hydroxy-4- 9.4 phenyl-3(S)-{{N-(2-kino RINIRU - carbonyl) valyl} amino} butyl} -4(R)- {(2, 6-dimethyl-4-pyrimidinyl) oxy-} - Pyrrolidine-2(S)-carboxamide 13 N-tert-butyl-1-{3(S)-{{2, 6- 4.6 Dimethyl phenoxy acetyl} amino}-2(R)- Hydroxy-4-phenyl butyl}-4(R)- (2-pyrimidinyl thio)-pyrrolidine -2 (S) - The carboxamide 14 N-tert-butyl-1-{3(S)-{{2 and 6- 43 dimethyl phenoxy acetyl} amino} -2(R)- hydroxy-4-phenyl butyl}-4(R)- {(3-pilus JINIRU methyl) - thio} pyrrolidine - 2(S)-carboxamide [0052] Adaptation [the following procedure used in order to screen the anti-virus effectiveness of the compound of example 13 formula 1 / assay / using the cell which was already reported by above-mentioned Harada and others and by which the HTLV-I transformation was carried out / plaque]. Since the rate which HIV reproduces in a cell with it was quick, the cell by which the HTLV-I transformation was carried out was used.

1. Dissolve a trial compound into dimethyl sulfoxide and carry out concentration in 5mg/ml. The obtained solution can be stored at 4 degrees C to use.
2. Dilute the obtained solution in RPMI1640 (Gibco Laboratories, U.S. Massachusetts Lawrence), and make it into 4 times of the last concentration examined. If it dilutes in RPMI1640, this solution will be used within 4 hours in cell culture assay.
3. This 4X solution (50microl) was added to 3 section well of the flat bottom fine titration plate of 96 wells. RPMID (50microl) is added also to a contrast well.
4. RPMI1640(pH=7.2) 50microL by which the HEPES buffer was carried out inner C -- the fetal calf serum (FCS) and 12.5microl/ml gentamycin (perfect medium) by which the heat inactive compound was carried out 10% are added to all wells 8166 cells (5x104).
5. Perfect-medium 100microl The H9-/HTLV-IIIB stock (saved in liquid nitrogen as cell culture supernatant liquid in 50%FCS) of inner 50 time TCID50 is added to all wells. The infection titration value of a virus stock is the same as what was beforehand determined by the terminal point dilution on C8166 cell. The titration value of a stock is stable for 6 to 12 hours, when saved in -193 degrees C.
[0053] 6. Subsequently, they are 37 degrees C and 5%CO2 about a fine titration plate. It puts on level shelving of the incubator made humid for 72 hours.
7. Subsequently, remove a plate and measure the core of the syncytium in each well with a low power phase optical microscope. Each cluster of the cell which shows the proof of formation of some syncytiums is measured as one core of syncytium. A contrast well has the core of the syncytium of 25-75 for every well.
8. Compute the inhibition percentage of syncytial formation by the following formula.
Inhibition (%) =100x {(syncytium core in the syncytium core-# trial well in # contrast well) /(syncytium core in # contrast well)}
The concentration 50 of the trial compound which brings about 50% inhibition of syncytial formation, i.e., EC, uses the serial dilution technique of the operation solution of a process 3, and it is determined by plotting the inhibition percentage by which the syncytial formation to the trial compound of various concentration was observed. In the following table 2, the result of the assay of the instantiation compound of the formula 1 obtained from the plaque assay of this example is shown.
[0054]
[Table 2]
A Table 2 number A compound EC50 (nM) 1 4 (R) - Benzyloxy-1-{3(S)-{{N- 600 Valyl}-amino}-(Benzyloxycarbonyl) 2(R)-hydroxy-4-phenyl butyl}-N- The tert-butyl-pyrrolidine-2(S)-carboxamide 2 4 (R) - Benzyloxy-1-{3(S)-{{N- 600 Benzyloxycarbonyl asparaginyl} amino}-2(R)-hydroxy-4-phenyl butyl}-N-tert-butyl-pyrrolidine-2(S)-carboxamide 3 1-{3(S)-{{N-(benzyloxycarbonyl)- 3000 Valyl} amino}-2(R)-hydroxy-4- Phenyl butyl}-N-tert-butyl -4 (R) - () [2-] Methylpropyl oxy-pyrrolidine -2 (S) - The carboxamide 4 4 (R) - Benzyloxy-1-{3(S)-{{N- 900 (Benzyloxycarbonyl) Valyl} amino}- 2(R)-hydroxy-4-phenyl butyl}-N- The cyclo propyl pyrrolidine-2(S)-carboxamide 5 3(S)-{{the N- 700 (benzyloxycarbonyl) asparaginyl}- 4(R)-benzyl-1- {-- The amino}-2(R)-hydroxy-4-phenyl butyl}-N-tert-butyl-pyrrolidine-2(S)-carboxamide 6 4(S)-benzyl-1-{3(S)-{{N- 4000 Asparaginyl} amino}- (Benzyloxycarbonyl) 2(R)-hydroxy-4-phenyl butyl}-N- The tert-butyl-pyrrolidine-2(S)-carboxamide 7 N-tert-butyl-1-{2(R)-hydroxy-4- 250 phenyl-3(S)-{{N - () [2-kino RINIRU-] Carbonyl valyl} amino} butyl}-4(R)- (2-pyrimidinyl thio) - pyrrolidine -2 (S) - Carboxamide 8 N-tert-butyl-1-{2(R)-hydroxy-4- 480 Phenyl-3(S)-{{N - () [2-kino RINIRU-] Carbonyl valyl} amino} butyl}-4(R)- {(3-pilus JINIRU methyl) - thio} pyrrolidine - The 2(S)-carboxamide 9 N-tert - Butyl-1-{2(R)-hydroxy-4- 390 phenyl - three -- (-- S --) - {-- {-- N - (2-kino RINIRU-carbonyl) -- the valyl --} -- amino --} -- butyl --} -4 (R) - The {(2, 6-dimethyl-4-pyrimidinyl) oxy-

}-pyrrolidine-2(S)-carboxamide 10 N-tert-butyl-1- {3(S)-{{2 and 6-250 dimethyl phenoxy acetyl} amino}-2 (R)-hydroxy-4-phenyl butyl --} -4 (R) - () [2-] pyrimidinyl thio-pyrrolidine -2 (S) - Carboxamide [0055] there are the following in the compound of others of a formula 1 -- :N-tert-butyl-1-{2(R)-hydroxy-4-phenyl-3(S)-{{N-(2-KINORI nil carbonyl) valyl} amino} butyl} -4(R)-(phenyl sulfonyl) pyrrolidine-2 (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- (2-KINORI nil carbonyl) Valyl} amino} butyl} -4 (R) - A pyrrolidine -2 (2-PIRIJI nil thio) (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- (2-KINORI nil carbonyl) Valyl} amino} butyl} -4 (R) - A pyrrolidine -2 (4-PIRIJI nil thio) (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- (2-KINORI nil carbonyl) Valyl} amino} butyl} -4 (R) - A pyrrolidine -2 (4, 6-dimethyl-2-pyrimidinyl thio) (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- (2-pilus JINIRU carbonyl) Valyl} amino} butyl} -4 (R) - phenoxy pyrrolidine -2 (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl - 3 (S) -{{N- (2-pilus JINIRU carbonyl) Asparaginyl} amino} butyl}-4(R)-phenoxy pyrrolidine -2 (S) - Carboxamide N-cyclopentyl-1-{2(R)-HIDO ROKISHI - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- leucyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenyl sulfonyl) -- a pyrrolidine - two -- (-- S --) - cull -- BOKISA MIDO [0056] 1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N-Valyl} amino} butyl}-N- (2-KINORI nil carbonyl) (1-methylethyl) -4 (R) - A pyrrolidine -2 (2-PIRIJI nil thio) (S) - carboxamide N-cyclo propyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- 2(R)-hydroxy-4-phenyl [N-tert-butyl-1-{] -3 (S)-{{N- (2-KINORI nil carbonyl) asparaginyl} amino} -- the butyl}-4(R)-(4-PIRIJI nil thio) pyrrolidine-2(S)-carboxamide -- 2(R)-hydroxy-4-phenyl [N-tert-butyl-1-{] -3 (S)-{{N- (2-KINORI nil carbonyl) isoleucyl} amino} -- the butyl}-4(R)-(2-pyrimidinyl thio) pyrrolidine-2(S)-carboxamide -- (2-naphthyl carbonyl) Valyl} amino} butyl} -4 (R) - A pyrrolidine -2 (4, 6-dimethyl-2-pyrimidinyl thio) (S) - carboxamide N-tert-butyl-1-{2 (R) - hydroxy-4-phenyl -3 (S) -{{N- (2-pilus JINIRU carbonyl) isoleucyl} amino} butyl}-4(R)-phenoxy pyrrolidine -2 (S)-carboxamide N-tert-butyl-1-{2(R)-hydronalium KISHI - four - phenyl - three -- (-- S --) - {-- {-- N - (2-pilus JINIRU carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenylthio) -- a pyrrolidine - two -- (-- S --) - the carboxamide

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[Translation done.]

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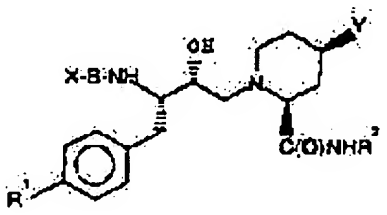
(54) SUBSTITUTED PIPECOLINIC ACID DERIVATIVE AND HIV PROTEASE INHIBITOR

(57)Abstract:
PURPOSE: To obtain substituted pipecolinic acid derivatives useful for treatment of HIV infections, inhibiting the activity of HIV protease and suppressing cytopathogenic effects induced by HIV in human cells.
CONSTITUTION: This compound of formula I [X is R3OC(O), R3C(O) or R3NR4C (O) (R3 is alkyl, cycloalkyl, phenyl, naphthyl or the like; R4 is H or alkyl) or the like; B is absent or NHCHR5C(O) (R5 is alkyl, cycloalkyl, phenylmethyl or the like); R1 is H, halogen, OH, alkyl or alkoxy; R2 is alkyl; Y is alkyl, cycloalkyl, phenyl or W(CH2)nZ (W is O, S, SO or SO2; Z is alkyl, substituted phenyl or the like; n is 0 or 1) or the like] e.g. N-tert-butyl-1-{3(S)- benzyloxycarbonylamino}-2(R)-hydroxy-4-phenylbutyl}-4(R)-phenylpiperidine-2(S) carboxamide is obtained, when B is absent, by reaction of a compound of formula II with a compound of formula III.



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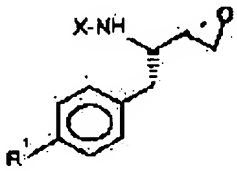


II

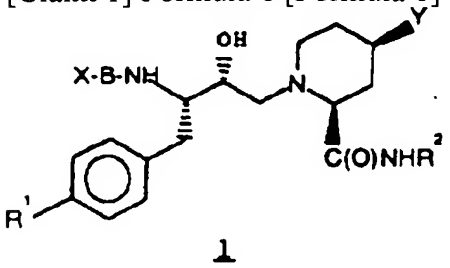
III

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

CLAIMS

[Claim(s)]
[Claim 1] Formula 1 [Formula 1]



1

The compound come out of and shown, or its acid addition salt which may be permitted in thrapeutics. [-- however, the inside of a formula and X -- R3 OC (O), R3 C (O), or R3 NR4 C (O) -- it is (R3 among a formula) (i) Low-grade alkyl and (ii) low-grade cycloalkyl (iii) Phenyl; [Halogen,] The phenyl whose each of phenyl; carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI or two substituents is low-grade alkyl or a halogen independently and which was carried out 2 ****s, (iv) Phenyl (low-grade) alkyl or its aromatic series part Halogen, The phenyl (low-grade) alkyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI, (v) 1-naphthyl or 2-naphthyl, (vi) (Het), or (Het) -(low-grade alkyl) (Het among a formula) the univalent heterocycle radical of 5 containing the hetero atom of 1 or 2 chosen from nitrogen, oxygen, and sulfur or 6 members is shown -- or (vii) -- They are 2-kino RINIRU or 3-kino RINIRU. And R4; or X which is hydrogen or low-grade alkyl It is R3AOCH2 C (O) (R3A among a formula). ;B which is one permutation phenyl or each substituent of whose is low-grade alkyl or a halogen independently, two permutations, or the phenyl carried out 3 ****s They are whether it exists and divalent radical-NHCHR5 C(O)- (among a formula). R5 hydroxy ** low-grade alkyl; -- low-grade cycloalkyl; (low-grade cycloalkyl) -(low-grade alkyl); phenylmethyl; -- or it is the low-grade alkyl carried out by 1 **** of carboxy, low-grade alkoxy carbonyl, aminocarbonyl, aminocarbonyl (low-grade alkyl), or JI (low-grade alkyl) aminocarbonyl --;R1 hydrogen, a halogen, hydroxy ** low-grade alkyl, or those with low-grade alkoxy ** --;R2 low-grade alkyl -- it is --; and Y -- low-grade alkyl; -- low-grade -- cycloalkyl; phenyl or a halogen -- Phenyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI; Phenylmethyl or a halogen, It is phenylmethyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI.; or Y It is W(CH2) n Z (W is oxo-** thio, sulfinyl, or a sulfonyl among a formula Z). low-grade -- phenyl; carried out by 1 **** of alkyl; phenyl or a halogen, hydroxy ** low-grade alkyl, or low-grade ARUKOKISHI -- or (Het) -- it is (the inside of a formula and (Het) are as the above-mentioned definition) --;n is 0 or 1.]
[Claim 2] The inside of a formula and X are R3 OC (O), R3 C (O), or R3 NR4 C (O) (R3 among a formula). Low-grade alkyl, phenyl, 2, 4-dimethylphenyl, 2, 6-dimethylphenyl, 2, 4-dichlorophenyl, 2, 5-dichlorophenyl, 2, 6-difluoro phenyl, 5-fluoro-2-methylphenyl, phenyl (low-grade) alkyl, and phenyl (low-grade) alkyl (the 4th place of a phenyl part -- chloro --) Fluoro, hydroxy ** methyl, or methoxy permutes. 1-naphthyl, 2-naphthyl, 2-furil, 2-thienyl, 2-pyridinyl ; or X whose R4 it is 4-pyridinyl 2-pilus JINIRU methyl, 4-thiazolyl methyl, or 2-kino RINIRU, and is hydrogen or low-grade alkyl It is R3AOCH2 C (O) (R3A among a formula). In the location or two or more locations of 1 chosen from the group which consists of phenyl or 2 and 4, and the 6th place,;B which is 1, 2, or the phenyl carried out 3 ****s with low-grade alkyl or a halogen It does not exist or is divalent radical-NHCHR5 C(O)- (R5 among a formula). Low-grade alkyl or hydroxy ** low-grade alkoxy carbonyl, aminocarbonyl, (Low-grade alkyl) it is the low-grade alkyl carried out by 1 **** of aminocarbonyl or JI (low-grade alkyl) aminocarbonyl --;R1 hydrogen, chlorine, a

bromine, and a fluorine -- it is --;R2 It is 1-methylethyl, 2-methylpropyl or 1, and 1-dimethyl ethyl.; and Y Low-grade cycloalkyl, phenyl, 4-chlorophenyl, 4-BUROMO phenyl, 4-fluoro phenyl, 4-methylphenyl, 4-methoxypheny, They are phenylmethyl, methyl (4-fluoro phenyl), or (4-methylphenyl) methyl.; or Y It is W (CH2) n Z (W and n are as the above-mentioned definition among a formula). Z Low-grade alkyl, phenyl, 2-furil, 2-thienyl, 2-pyridinyl The compound according to claim 1 which is 3-pyridinyl 4-pyridinyl 4-thiazolyl, 2-pyrimidinyl, 4-methyl-2-pyrimidinyl, 4, and 6-dimethyl-2-pyrimidinyl or 2, and 6-dimethyl-4-pyrimidinyl, or its acid addition salt which may be permitted in thrapeutics.

[Claim 3] X among a formula tert-butyloxy carbonyl, carbonyl (2, 6-dimethylphenyl), Carbonyl, carbonyl (2, 5-dichlorophenyl), (2, 4-dichlorophenyl) Carbonyl, carbonyl (5-fluoro-2-methylphenyl), (2, 6-difluoro phenyl) Benzyloxycarbonyl, methoxycarbonyl (4-chlorophenyl), Methoxycarbonyl, methoxycarbonyl (4-methoxypheny), (4-hydroxyphenyl) Acetyl, benzoyl, 1-North America Free Trade Agreement RENIRU carbonyl, 2-North America Free Trade Agreement RENIRU carbonyl, Carbonyl, 2-KINORI nil carbonyl, (2-pilus JINIRU methoxy) Benzylamino carbonyl, N-(2-pilus JINIRU methyl) aminocarbonyl, N-methyl-N-(2-pilus JINIRU methyl) aminocarbonyl, phenoxy acetyl, Acetyl, acetyl (2, 4-dimethyl phenoxy), (2-methylphenoxy) Acetyl, acetyl (2, 4, 6-trimethyl phenoxy), (2, 6-dimethyl phenoxy) They are acetyl or (the 4-fluoro -2, 6-dimethyl phenoxy) acetyl. (4-chloro phenoxy);B It does not exist or is divalent radical-NHCHR5 C(O)- (R5 among a formula). 1-methylethyl, 1, and 1-dimethyl ethyl, 1-methylpropyl, 2-methylpropyl, 1-hydroxyethyl, methyl (methoxycarbonyl), (Ethoxycarbonyl) methyl, methyl (aminocarbonyl), or {(methylamino) carbonyl} methyl -- it is --;R1 It is hydrogen or a fluorine and is;R2. It is 2-methylpropyl or 1, and 1-dimethyl ethyl.; and Y Cyclohexyl, phenyl, 4-chlorophenyl, 4-fluoro phenyl, 4-methoxypheny, benzyl, methyl (4-methoxypheny), 2-methyl propoxy, phenoxy, and 2-pilus JINIRU oxy-**3-pilus JINIRU oxy-** 4-pilus JINIRU oxy-**2-pyrimidinyl oxy-** (4-methyl-2-pyrimidinyl) oxy-** Oxy-** (2, 6-dimethyl-4-pyrimidinyl) oxy-** (4, 6-dimethyl-2-pyrimidinyl) Benzyloxy one, 2-pilus JINIRU methoxy, 3-pilus JINIRU methoxy, 4-pilus JINIRU methoxy, 4-thiazolyl methoxy, phenylthio, Phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, Thio, thio (2, 6-dimethyl-4-pyrimidinyl), (4-methyl-2-pyrimidinyl) Thio, benzyl thio, benzyl sulfinyl, (4, 6-dimethyl-2-pyrimidinyl) The compound according to claim 2 which is a benzyl sulfonyl, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or (4-pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 4] X among a formula tert-butyloxy carbonyl, benzyloxycarbonyl, Acetyl, carbonyl (2, 6-dimethylphenyl), 2-North America Free Trade Agreement RENIRU carbonyl, They are carbonyl, 2-KINORI nil carbonyl, or {N-methyl-N-(2-pilus JINIRU methyl) amino} carbonyl. (2-pilus JINIRU methoxy);B the valyl, tert-butyl glycyl, the isoleucyl, threo nil, or the asparaginyl -- it is --;R1 It is hydrogen or a fluorine and is;R2. It is 1 and 1-dimethyl ethyl.; and Y Phenyl, benzyl, phenoxy, and 2-pyrimidinyl oxy-** (2, 6-dimethyl-4-pyrimidinyl) oxy-** 2-pilus JINIRU methoxy, 3-pilus JINIRU methoxy, 4-pilus JINIRU methoxy, Phenylthio, phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, (4, 6-dimethyl-2-pyrimidinyl) The compound according to claim 3 which is thio, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or 4-(pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 5] X among a formula Acetyl (2-methylphenoxy), (2 and 4-dimethyl phenoxy)-acetyl, (2, 6-dimethyl phenoxy) acetyl or (2, 4, 6-dimethyl phenoxy) acetyl -- it is --;B -- not existing --;R1 hydrogen -- it is --;R2 It is 1 and 1-dimethyl ethyl.; and Y Phenyl, benzyl, phenoxy, 2-pyrimidinyl oxy-**2-pilus JINIRU methoxy, 3-pilus JINIRU methoxy, 4-pilus JINIRU methoxy, phenylthio, phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, (4, 6-dimethyl-2-pyrimidinyl) The compound according to claim 3 which is thio, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or (4-pilus JINIRU methyl) thio, or its acid addition salt which may be permitted in thrapeutics.

[Claim 6] N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-(4-fluoro phenyl) butyl}-4(R)-(phenylthio) piperidine-2(S)-carboxamide -- N-tert-butyl-1-{3 (S) - (Benzyloxycarbonylamino) -2 (R) - hydroxy-4-phenyl butyl}-4 (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - (benzyloxycarbonylamino) - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - benzyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(phenyl sulfonyl) piperidine-2(S)-carboxamide -- N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(phenylthio) piperidine-2(S)-carboxamide -- N-tert-butyl-1- the {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-phenoxy piperidine-2(S)-carboxamide -- N-tert-butyl-1- the {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-cyclohexyl

piperidine-2(S)-carboxamide -- N-tert - butyl - one - {- three -- (-- S --) - {-- {-- N - benzyloxycarbonyl - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the isoleucyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - benzyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (phenyl sulfonyl) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert-butyl-1-{3 (S) -{{N- (Benzyloxycarbonyl) - asparaginyl} amino}-2 (R) - hydroxy-4-phenyl butyl}-4 (R) - A piperidine -2 (Phenyl sulfonyl) (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - phenoxy -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - phenoxy -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-piperidinyloxy) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - cyclohexyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert-butyl-1- {-- 2(R)-hydroxy-4-phenyl -3 (S) - {-- {(N-(2-KINORI nil carbonyl) valyl} amino} butyl} -- the -4(R)-(phenylthio) piperidine-2(S)-carboxamide --) N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenoxy -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert-butyl-1- {2(R)-hydroxy-4-phenyl-3(S)-{{N-(2-KINORI nil carbonyl) asparaginyl} amino} butyl} -4 (R) - (phenyl sulfonyl) -- PIPERIJI N - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-North America Free Trade Agreement RENIRU carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - three -- (-- S --) - {-- {-- N - (2-North America Free Trade Agreement RENIRU carbonyl) -- the asparaginyl --} -- amino --} - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - (4-fluoro phenyl) -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - {(2-pilus JINIRU methoxy) -- carbonyl --} -- the isoleucyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(2-PIRIJI nil thio) piperidine-2(S)-carboxamide -- N-tert-butyl-1-{3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(4-PIRIJI nil thio)- the piperidine-2(S)-carboxamide -- N- tert-butyl-1-{3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(2-pyrimidinyl thio)- the piperidine-2(S)-carboxamide -- N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(4, 6-dimethyl-2-pyrimidinyl thio) piperidine-2(S)-carboxamide -- N-tert-butyl -1 -- the - {3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-(benzyl thio) piperidine-2(S)-carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --

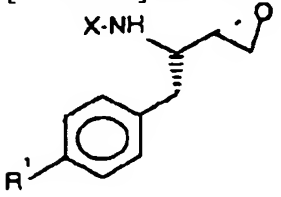
) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4, 6-dimethyl-2-pyrimidinyl thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (benzyloxycarbonyl) - the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (benzyl thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - three -- (-- S --) - {-- N - {-- [-- N - methyl - N - (2-pilus JINIRU methyl) -- amino --] -- carbonyl --} -- the valyl --} - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4-pilus JINIRU methyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pilus JINIRU methoxy) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4, 6-dimethyl-2-pyrimidinyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two - the carboxamide -- N-tert-butyl-1-{2(R)-hydroxy-4-phenyl-3(S)-{{N-(2-KINORI nil carbonyl) valyl} amino} butyl} -4 (R) - (2-pilus JINIRU) thio -- a piperidine - two - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenoxy - a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2-pilus JINIRU methyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pyrimidinyl oxy-) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4, 6-dimethyl-2-pyrimidinyl) -- oxy-one --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4-methyl-2-pyrimidinyl) -- oxy-one --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2, 6-dimethyl-4-pyrimidinyl) -- oxy-one --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenyl sulfonyl) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4-fluoro phenyl) -- oxy-one --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (4-pilus JINIRU methoxy) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2-pilus JINIRU methyl) -- a sulfonyl --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- a sulfonyl --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4-pilus JINIRU methyl) -- a sulfonyl --} -- a piperidine - two - the carboxamide -- N-

tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pilus JINIRU sulfonyl) - - a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (4-pilus JINIRU sulfonyl) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(2, 6-dimethyl-4-pyrimidinyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4-methyl-2-pyrimidinyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (3-pilus JINIRU methoxy) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) - tert - butyl -- glycyl --} -- amino --} -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(4, 6-dimethyl-2-pyrimidinyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a piperidine - two - the carboxamide -- N-tert-butyl-1-{2(R)-hydroxy-4-phenyl-3(S)-{{N-(2-KINORI nil carbonyl)-N4 - The methyl-asparaginyl} amino} butyl}-4(R)-phenoxy-piperidine-2-carboxamide, N-tert - butyl - one - {-- two - - (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) - tert - butyl -- glycyl --} -- amino --} -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy ones - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- threo -- nil --} -- amino --} -- butyl --} - four -- (-- R --) - (phenyl sulfonyl) -- a piperidine - two - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) - tert - butyl -- glycyl --} -- amino --} -- butyl --} - four -- (-- R --) - (4-pilus JINIRU sulfonyl) -- a piperidine - two - the carboxamide -- N - tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) - tert - butyl -- glycyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pilus JINIRU sulfonyl) -- a piperidine - two - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {(2, 6-dimethyl phenoxy) -- acetyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- three -- (-- S --) - {-- {(2, 4, 6-trimethyl phenoxy) - acetyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {(phenoxy acetyl) -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} -4 (R) - (4-PIRIJI nil thio) - the piperidine-2(S)-carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {(2, 6-dimethyl phenoxy) -- acetyl --} - amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {(2-methylphenoxy) -- acetyl --} - amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- two -- four - dichlorophenyl -- carbonyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- two --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {(2, 5-dichlorophenyl) -- carbonyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- three -- (-- S --) - {-- {(2, 6-difluoro phenyl) -- carbonyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- And N-tert-butyl-1-{3 (-- S --) - {-- {(5-fluoro-2-methylphenyl) -- carbonyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four - - (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- from -- becoming -- a group -- from -- choosing -- having -- being according to claim 1 -- a compound .

[Claim 7] The pharmacological constituent containing a compound according to claim 1 or its salt which may be permitted in thrapeutics, and the support which may be permitted pharmacologically.

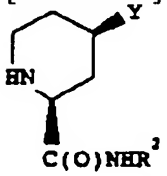
[Claim 8] How to treat a human HIV infectious disease including medicating Homo sapiens with the compound or its salt which may be permitted in thrapeutics of an effective dose according to claim 1.

[Claim 9] How to protect a human cell including processing a human cell by the compound or its salt which may be permitted in thrapeutics of an anti-HIV effective dose according to claim 1 from a HIV pathogen.
[Claim 10] the Following Process:(a) type 2 -- [Formula 2]



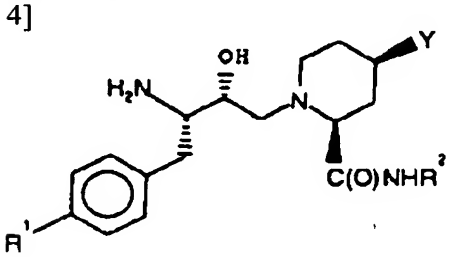
2

the epoxide of (the inside of a formula, and X and R1 are as having defined claim 1), and a formula 3 -- [Formula 3]



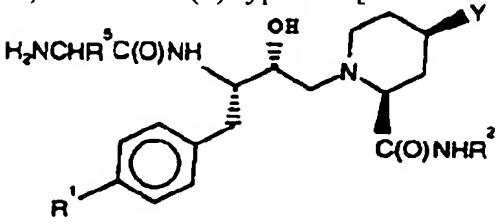
3

or [obtaining the compound with which the piperidine carboxamide of (the inside of a formula, R2, and Y are as having defined claim 1) is made to react, and a formula 1 (X, R1, R2, and Y are as the above-mentioned definition among a formula, and B does not exist) corresponds] --; or the (b) type 4 -- [Formula 4]



4

It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R2, and Y are as the above-mentioned definition). The reactant derivative of being R3 C (O) of the above-mentioned definition or R3AOCH2 C (O) is made to react. Formula 1 (X is R3 C [of the above-mentioned definition] (O), or R3AOCH2 C (O) among a formula) The corresponding compound with which R1, R2, and Y are as the above-mentioned definition, and B does not exist is obtained, or they are; or the (c) type 4 (R1, R2, and Y among a formula). The compound and formula X-NHCHR5 COOH (X and R5 among a formula) of being as the above-mentioned definition Coupling of the alpha-amino acid of being as the definition of claim 1 is carried out under existence of a coupling agent, and it is a formula 1 (X, R1, R2, and Y among a formula). or [obtaining the corresponding compound of it being as the above-mentioned definition and B being divalent radical-NHCHR5 C(O)- (the inside of a formula and R5 being as the above-mentioned definition)] --; -- or -- the (d) type 5 -- [Formula 5]



5

It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R2, R5, and Y are as the above-mentioned definition). The reactant derivative of being R3 C (O) of the above-

mentioned definition or R3AOCH2 C (O) is made to react, and it is a formula 1 (X). It is R3 C (O) of the above-mentioned definition, or R3AOCH2 C (O), and is R1 and R2. And Y the corresponding compound of it being as the above-mentioned definition and B being divalent radical-NHCHR5 C(O)- (the inside of a formula and R5 being as the above-mentioned definition) -- obtaining --; -- subsequently (e) How to manufacture the compound or the acid addition salt which may be permitted in thrapeutics including changing the compound of the formula 1 obtained by the request in the above-mentioned section (a), (b), (c), or (d) into the corresponding acid addition salt which may be permitted in thrapeutics of the formula 1 according to claim 1.

[Translation done.]

* NOTICES *

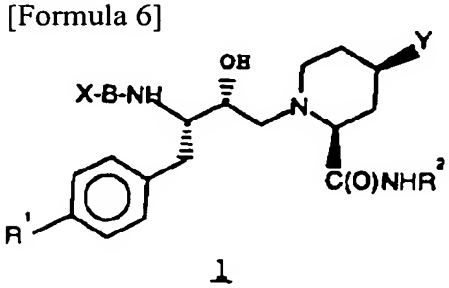
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the operation of the compound for repulsing the infectious disease produced by the compound in which the activity over a specific retrovirus is shown, the manufacture approach of the compound, its pharmacological formula object, and the retrovirus.
[0002]
[Description of the Prior Art] The retrovirus known as a human immunodeficiency virus type 1 (HIV-1) in 1983 was established as a pathogen of acquired immunodeficiency **** (acquired immunode-ficiency syndrome). R.C. Galo and "Scientific American" by L. MONTANI yell, 259 (4), 40 (1988) reference. This virus serves as an epidemic like making fear have. Recently, the virus and the human immunodeficiency virus type 2 (HIV-2) which are related very much are identified more as the 2nd pathogen of an acquired immunode-ficiency syndrome. The compound which checks the duplicate of HIV in the outside of a living body is discovered by identifying the human immunodeficiency virus (HIV) as a pathogen, and developing the approach of growing up this virus in large quantities. the most important class of inhibition compound identified by this approach -- the group of a dideoxy nucleoside -- it is -- that 3'-azide-3'-deoxythymidine (known also as zidovudine or AZT) -- and more, 2'3'-dideoxyinosine (known also as didanosine or DDI) is used in thrapeutics, and, recently, has managed the specific patient according to a **** HIV infectious disease. When this kind of compound checks reverse transcription, barring the life cycle of HIV is discovered. This enzyme converts Virus RNA into a double strand deoxyribonucleic acid (DNA), and is an indispensable enzyme for a HIV duplicate in itself. Besides inhibition of reverse transcription, the term of others of a HIV life cycle is identified as a target for development of anti-HIV medicine. The target of 1 which has received increasing cautions is an enzyme which is known as a HIV protease and by which the HIV code was carried out. Like reverse transcriptase, the code of this enzyme is carried out by the pol gene, and it is indispensable to growth of HIV. This is a causative agent which emits the enzyme containing the structural protein (for example, p17 and p24) and itself which perform specific division in gag (p55) or gag-pol (p180) protein, and are seen in mature infectivity virion. Therefore, the inhibitor of a HIV protease can block a HIV life cycle.
[0003] The increment in the interest with which the HIV protease was filled is reflected in the increment in a report of discovery of the matter which checks an enzyme over the past several years. For example, refer to the paper of the bacteria about D.W. Nor Bec and D.J. kemp, "Annual Reports In Medicinal Chemistry", and the protease inhibitor by 26,141 (1991). As the latter paper is indicated and it is reported by J. D.H. Rich et al., "Med.Chem.", 33 and 1285 (1990) and N.A. Roberts et al., "Science", and 248 and 358 (1990) Two powerful HIV protease inhibitor systems are understood by arranging a hydroxy ethylamine transition state prototype (TSA) in the peptide which has p17 / p24 substrate decomposition part array. biological research of the lead compound of continuation of Roberts and others -- H.A. exaggerated tons, "Virology", 179 and 508 (1990), J.A. Martin et al., and "Biochem.Biophys.Res.Commun." -- it is reported by 176, 180 (1991) and J.C. Craig et al., "Antiviral Chemistry and Chemotheraphy", and 2,181 (1991). An indication of others of the HIV protease inhibitor which has the hydroxy ethylamine TSA : which includes the following -- B.K. pewters and the Europe patent application No. 346847 published on December 20, 1989 G. B. DOREIYA et al., Europe patent application No. 352000 published on January 24, 1990, D. J. kemps, Europe patent application No. 402646 published on December 19, 1990, K -- the E.B. Per Cars et al., the Canadian patent application No. 2,030,415 published on June 12, 1991, J.A. Martin and S. red show, and the Europe patent application No. 432695 published on June 19, 1991.
[0004]

[Elements of the Invention] This application indicates the permutation pipecolic acid (pipecolinic acid) derivative which has the ethylamine TSA introduced into it. These derivatives are the powerful inhibitors of a HIV protease. Furthermore, the capacity which checks the cytopathogenic effectiveness by which HIV induction was carried out in the human cell is shown about these compounds. Since it has comparatively alternative operation and property that no toxicity is clearly, in these property lists, the compound is effective as drugs for repulsing a HIV infectious disease. The compound of this invention is a formula 1 [0005].

[Formula 6]



1

[0006] It is the acid addition salt which comes out, is shown or may be permitted in thrapeutics. However, the inside of a formula and X are R3 OC (O), R3 C (O), or R3 NR4 C (O) (R3 among a formula). (i) Low-grade alkyl and (ii) low-grade cycloalkyl (iii) Phenyl; [Halogen,] The phenyl;(iv) phenyl (low-grade) alkyl or the aromatic series part whose each of two substituents is low-grade alkyl or a halogen independently and which was carried out 2 ****s Phenyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI; A halogen, hydroxy ** The phenyl (low-grade) alkyl carried out by 1 **** of low-grade alkyl or low-grade ARUKOKISHI, (v) 1-naphthyl or 2-naphthyl, (vi) (Het), or (Het) - (low-grade alkyl) (Het) The univalent heterocycle radical of 5 containing the hetero atom of 1 or 2 chosen from nitrogen, oxygen, and sulfur or 6 members is shown. or (vii) 2-kino RINIRU or 3-kino RINIRU -- it is -- R4 [and] ; or X which is hydrogen or low-grade alkyl is R3AOCH2 C (O) (inside of formula and R3A is one permutation phenyl or each substituent of whose is low-grade alkyl or a halogen independently, two permutations, or the phenyl carried out 3 ****s).;

[0007] B is whether it exists and divalent radical-NHCHR5 C(O)- (among a formula). R5 hydroxy ** low-grade alkyl; -- low-grade cycloalkyl; (low-grade cycloalkyl) -(low-grade alkyl); phenylmethyl; -- or it is the low-grade alkyl carried out by 1 **** of carboxy, low-grade alkoxy carbonyl, aminocarbonyl, aminocarbonyl (low-grade alkyl), or JI (low-grade alkyl) aminocarbonyl --;R1 hydrogen, a halogen, hydroxy ** low-grade alkyl, or those with low-grade alkoxy ** --;R2 low-grade alkyl -- it is --; and Y -- low-grade alkyl; -- low-grade -- cycloalkyl; phenyl or a halogen -- Phenyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI; Phenylmethyl or a halogen, It is phenylmethyl carried out by 1 **** of hydroxy ** low-grade alkyl or low-grade ARUKOKISHI.; or Y It is W(CH2) n Z (W is oxo- ** thio, sulfinyl, or a sulfonyl among a formula Z). low-grade -- phenyl; carried out by 1 **** of alkyl; phenyl or a halogen, hydroxy ** low-grade alkyl, or low-grade ARUKOKISHI -- or (Het) -- it is (the inside of a formula and (Het) are as the above-mentioned definition) --;n is 0 or 1.

[0008] the phrase "B does not exist" used by this detail letter about a formula 1 should understand that it means that Notation B serves as covalent bond which combines "X" with the 2nd amino group (it combines with "B" in the case of others). The suitable group of the compound of this invention is a formula 1 (X among a formula). They are R3 OC (O), R3 C (O), or R3 NR4 C (O) (R3 among a formula). Low-grade alkyl, phenyl, 2, 4-dimethylphenyl, 2, 6-dimethylphenyl, 2, 4-dichlorophenyl, 2, 5-dichlorophenyl, 2, 6-difluoro phenyl, The 4th place of 5-fluoro-2-methylphenyl, phenyl (low-grade) alkyl, and a phenyl part Chlorine, The phenyl (low-grade) alkyl permuted by a fluorine, fluoro, hydroxy ** methyl, or methoxy, 1-naphthyl, 2-naphthyl, 2-furil, 2-thienyl, 2-pyridinyl 4-pyridinyl 2-pilus JINIRU methyl, 4-thiazolyl methyl, or 2-kino RINIRU -- it is -- R4 they are hydrogen or low-grade alkyl --; -- or -- X It is R3AOCH2 C (O) (inside of formula and R3A is 1, 2, or the phenyl carried out 3 ****s by low-grade alkyl or the halogen in the location or two or more locations of 1 chosen from the group which consists of phenyl or 2 and 4, and the 6th place).;

[0009] B does not exist or is divalent radical-NHCHR5 C(O)- (R5 among a formula). Low-grade alkyl or hydroxy ** low-grade alkoxy carbonyl, aminocarbonyl, (Low-grade alkyl) it is the low-grade alkyl carried out by 1 **** of aminocarbonyl or JI (low-grade alkyl) aminocarbonyl --;R1 hydrogen, chlorine, a bromine, or a fluorine -- it is --;R2 It is 1-methylethyl, 2-methylpropyl or 1, and 1-dimethyl ethyl.; and Y Low-grade

cycloalkyl, phenyl, 4-chlorophenyl, 4-BUROMO phenyl, 4-fluoro phenyl, 4-methylphenyl, 4-methoxypheny, They are phenylmethyl, methyl (4-fluoro phenyl), or (4-methylphenyl) methyl.; or Y It is W (CH2) n Z (W and n are as the above-mentioned definition among a formula). Z Low-grade alkyl, phenyl, 2-furil, 2-thienyl, 2-pyridinyl 3-pyridinyl 4-pyridinyl 4-thiazolyl, 2-pyrimidinyl, 4-methyl-2-pyrimidinyl, 4, and 6-dimethyl-2-pyrimidinyl or 2, and 6-dimethyl-4-pyrimidinyl -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics.

[0010] The more desirable group of the compound of this invention is a formula 1 (X among a formula). tert-butyloxy carbonyl, carbonyl (2, 6-dimethylphenyl), Carbonyl, (2 and 5-dichlorophenyl)-carbonyl, (2, 4-dichlorophenyl) Carbonyl, carbonyl (5-fluoro-2-methylphenyl), (2, 6-difluoro phenyl) Benzyloxycarbonyl, MEOKISHI (4-chlorophenyl) carbonyl, Methoxycarbonyl, methoxycarbonyl (4-methoxypheny), (4-hydroxyphenyl) Acetyl, benzoyl, 1-North America Free Trade Agreement RENIRU carbonyl, 2-North America Free Trade Agreement RENIRU carbonyl, Carbonyl, 2-KINORI nil carbonyl, (2-pilus JINIRU methoxy) Benzylamino carbonyl, N-(2-pilus JINIRU methyl) aminocarbonyl, N-methyl-N-(2-pilus JINIRU methyl) aminocarbonyl, phenoxy acetyl, Acetyl, acetyl (2, 4-dimethyl phenoxy), (2-methylphenoxy) Acetyl, acetyl (2, 4, 6-trimethyl phenoxy), (2, 6-dimethyl phenoxy) They are acetyl or (the 4-fluoro -2, 6-dimethyl phenoxy) acetyl. (4-chloro phenoxy);B It does not exist or is divalent radical-NHCHR5 C(O)- (R5 among a formula). 1-methylethyl, 1, and 1-dimethyl ethyl, 1-methylpropyl, It is 2-methylpropyl, 1-hydroxyethyl, methyl (methoxycarbonyl), methyl (ethoxycarbonyl), methyl (aminocarbonyl), or {(methylamino) carbonyl}-methyl, and is;R1. They are hydrogen or a fluorine.;

[0011] R2 It is 2-methylpropyl or 1, and 1-dimethyl ethyl.; and Y Cyclohexyl, phenyl, 4-chlorophenyl, 4-fluoro phenyl, 4-methoxypheny, benzyl, methyl (4-methoxypheny), 2-methyl propoxy, phenoxy, and 2-pilus JINIRU oxy-**3-pilus JINIRU oxy-** 4-pilus JINIRU oxy-**2-pyrimidinyl oxy-** (4-methyl-2-pyrimidinyl) oxy-** Oxy-** (2, 6-dimethyl-4-pyrimidinyl) oxy-** (4, 6-dimethyl-2-pyrimidinyl) Benzyloxy one, 2-pilus JINIRU methoxy, 3-pilus JINIRU methoxy, 4-pilus JINIRU methoxy, 4-thiazolyl methoxy, phenylthio, Phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, Thio, thio (2, 6-dimethyl-4-pyrimidinyl), (4-methyl-2-pyrimidinyl) Thio, benzyl thio, benzyl sulfinyl, (4, 6-dimethyl-2-pyrimidinyl) a benzyl sulfonyl, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or (4-pilus JINIRU methyl) thio -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics.

[0012] The most desirable group of a compound is a formula 1 (X among a formula). tert-butyloxy carbonyl, benzyloxycarbonyl, acetyl, Carbonyl, 2-North America Free Trade Agreement RENIRU carbonyl, (2, 6-dimethylphenyl) They are carbonyl, 2-KINORI nil carbonyl, or {N-methyl-N-(2-pilus JINIRU methyl) amino} carbonyl. (2-pilus JINIRU methoxy);B the valyl, tert-butyl glycyl, the isoleucyl, threo nil, or the asparaginyl -- it is --;R1 It is hydrogen or a fluorine and is;R2. It is 1 and 1-dimethyl ethyl.; and Y Phenyl, benzyl, phenoxy, and 2-pyrimidinyl oxy-** (2, 6-dimethyl-4-pyrimidinyl) oxy-** 2-pilus JINIRU methoxy, 3-pilus JINIRU methoxy, 4-pilus JINIRU methoxy, Phenylthio, phenyl sulfinyl, a phenyl sulfonyl, 2-PIRIJI nil thio, 3-PIRIJI nil thio, 4-PIRIJI nil thio, 2-pyrimidinyl thio, (4, 6-dimethyl-2-pyrimidinyl) thio, thio (2-pilus JINIRU methyl), thio (3-pilus JINIRU methyl), or 4-(pilus JINIRU methyl) thio -- it is -- it is the acid addition salt which is shown or may be permitted in thrapeutics.

[0013] The most desirable group of others of a compound is a formula 1 (X among a formula). Acetyl, acetyl (2, 4-dimethyl phenoxy), (2-methylphenoxy) (2, 6-dimethyl phenoxy) acetyl or 2 and 4, and 6-dimethyl-phenoxy acetyl -- it is --;B -- not existing --;R1 hydrogen -- it is --;R2 and as having defined Y immediately before -- it is -- or [being shown] -- or it is the acid addition salt which may be permitted in thrapeutics. It is related with the compound of a formula 1 (the inside of a formula and B are divalent radical-NHCHR5 C(O)-), and is R5. As for the asymmetric carbon atom to support, it is desirable to have (S) arrangement. The pharmacological constituent for the therapy of the human HIV infectious disease containing the compound of a formula 1 or its salt which may be permitted in thrapeutics, and the support which may be permitted by the pharmaceutical-sciences target is contained within the limits of this invention. The range of this invention also includes the approach of treating a human HIV infectious disease including medicating Homo sapiens with the compound of the formula 1 of an effective dose, or its salt which may be permitted in thrapeutics. The approach of protecting the human cell which includes processing a human cell by the compound of the formula 1 of an anti-HIV effective dose or its salt which may be permitted in thrapeutics again from a HIV pathogen is included by the range. The manufacture approach of the compound of a formula 1 is explained below. The abbreviation generally used in this specification in order to display amino acid and a protective group is based on advice of the biochemistry naming IUPAC-IUB committee. "European Journal of Biochemistry" 138, 9 (1984) reference. For example,

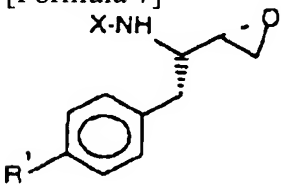
Val, Ile, Thr, Asn, and Leu show the residue of L-valine, L-isoleucine, L-threonine, L-asparagine, and L-leucine, respectively.

[0014] The independent or branched chain-like alkyl group containing the straight chain-like alkyl group and the carbon atom of 3-4 with which the phrase "low-grade alkyl" used in this specification combining the radical of 1 contains the carbon atom of 1-6 is meant, and methyl, ethyl, propyl, butyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl and 1, and 1-dimethyl ethyl is included. The independent or saturation cyclic hydrocarbon radical whose phrase "low-grade cycloalkyl" used in this specification combining the radical of 1 contains the carbon atom of 3-6 is meant, and cyclo propyl, cyclo butyl, cyclopentyl, and cyclohexyl are included. The phrase "low-grade alkoxy one" used in this specification means the alkoxy group of the shape of a branched chain containing the straight chain-like alkoxy group and the carbon atom of 3-4 containing the carbon atom of 1-6, and includes methoxy and ethoxy ** propoxy, HEKISOKISHI, 1-methylethoxy, butoxy and 1, and 1-dimethylethoxy. The latter radical is usually known as tert-butyloxy. The phrase "a halogen" used into this specification is a halogen radical chosen from a bromine, chlorine, a fluorine, and iodine. The phrase "residue" about amino acid means the radical obtained from the corresponding alpha-amino acid by removing the hydroxyl of a carboxy group, and the hydrogen of 1 of alpha-amino group. A phrase "tert-butyl glycyl" shows the amino acid residue of the 2(S)-amino -3 and 3-dimethyl butanoic acid, and a phrase "the N4-methyl asparaginyl" shows the amino acid residue of 2(S)-amino-4-methylamino-4-oxo-butanoic acid.

[0015] The phrase "Het" used into this specification is a univalent radical which hydrogen is removed and is obtained from the saturation or partial saturation heterocycle of 5 containing the hetero atom of 1-2 which are chosen from nitrogen, oxygen, and sulfur, or 6 members. To arbitration, this heterocycle may be supporting the substituent;, for example, low-grade alkyl, and low-grade alkoxy ** halogen, amino, or low-grade alkylamino of 1 or 2. The example of the heterocycle permuted by suitable heterocycle and arbitration includes pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1H-imidazole, 1-methyl-1H-imidazole, isoxazole, thiazole, 2-methyl thiazole, 2-aminothiazole, piperidine, 1, 4-dioxane, 4-morpholine, pyridine, 2-methylpyridine, pyrimidine, 4-methylpyrimidine and 2, and 4-dimethylpyrimidin. The phrase "the support which may be permitted pharmacologically" used into this specification does not give an operation harmful to an active ingredient, but it is [for an active ingredient] nonpoisonous and, generally it means an inactive excipient.

[0016] The phrase "an effective dose" used into this specification means the amount as which the compound of this invention effective enough was beforehand determined to HIV in in the living body. Generally, the reaction condition by which it is known that it is suitable for reagin is used for the compound of a formula 1, and it is manufactured by the learned approach. Edit according [the publication of an approach] to "Annual Reports In Organic Synthesis-1990" K. turn BAL, Academic Press, Incorporated, U.S. California San Diego, 1990 (and the above-mentioned "annual reports"), edit by "Vogel's Textbook of Practical Organic Chemistry" B.S. fur varnish, The long man group Limited, British Essex, 1986, and edit with "The peptides:Analysis, Synthesis, and Biology" E. glasses, A standard textbook like Academic Press, U.S. New York State New York, 1979-1987, and 1-9 volumes sees. When it explains especially, the compound of a formula 1 is the following process:(a) type 2 [0017].

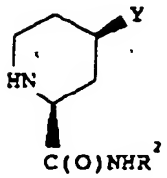
[Formula 7]



2

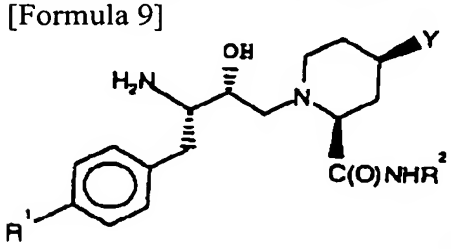
It is [the epoxide of (the inside of a formula, and X and R1 are as the above-mentioned definition), and] a formula 3 [0018].

[Formula 8]



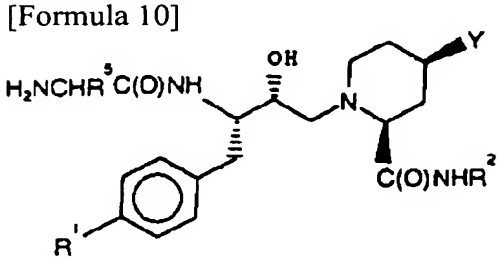
3

or [obtaining the compound with which the piperidine carboxamide of (the inside of a formula, R2, and Y are as the above-mentioned definition) is made to react, and a formula 1 (X, R1, R2, and Y are as the above-mentioned definition among a formula, and B does not exist) corresponds] --; -- or -- (b) type 4 [0019]
[Formula 9]



4

[0020] It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R2, and Y are as the above-mentioned definition). The reactant derivative of being R3 C (O) of the above-mentioned definition or R3AOCH2 C (O) is made to react. Formula 1 (X is R3 C [of the above-mentioned definition] (O), or R3AOCH2 C (O) among a formula) The corresponding compound with which R1, R2, and Y are as the above-mentioned definition, and B does not exist is obtained, or they are; or the (c) type 4 (R1, R2, and Y among a formula). The compound and formula X-NHCHR5 COOH (X and R5 among a formula) of being as the above-mentioned definition Coupling of the alpha-amino acid of being as the above-mentioned definition is carried out under existence of a coupling agent, and it is a formula 1 (X, R1, R2, and Y among a formula). They are [whether it is as the above-mentioned definition and B obtains the corresponding compound of being divalent radical-NHCHR5 C(O)- (the inside of a formula and R5 being as the above-mentioned definition), and]; or the (d) type 5 [0021].
[Formula 10]



5

[0022] It is [a compound and] carboxylic-acid X-OH (X among a formula) of (the inside of a formula, R1, R2, R5, and Y are as the above-mentioned definition). The reactant derivative of being R3 C (O) of the above-mentioned definition or R3AOCH2 C (O) is made to react, and it is a formula 1 (X). It is R3 C(O) R3AOCH2 C (O) or R3AOCH2 C (O), and is R1 and R2. And Y the passage of the above-mentioned definition -- it is -- B -- divalent radical-NHCHR5 C(O)- it is (the inside of a formula and R5 are as the above-mentioned definition) -- obtaining --; -- subsequently (e) It can be manufactured more by changing the compound of the formula 1 obtained by the request in the above-mentioned section (a), (b), (c), or (d) into the corresponding acid addition salt which may be permitted in thrapeutics. The kind of the compound of a formula 1 (the inside X of a formula is N-protective group usually used, for example, Boc and Z, Fmoc, or p-methoxybenzyloxy carbonyl) is acquired most easily and conveniently by a process (a) and (C). Since this kind is easy to come to hand easily, it is useful as intermediate field for the suitable path which manufactures each compound of a formula 1 (the inside X of a formula is except N-protective group usually used) through each process (b) and (d). As intermediate field, therefore, the compound of this kind of formula 1 The amino terminal isolation amine which deprotection was carried out (that is, a protective group is removed), and was subsequently obtained A final manufacture of the compound of a formula 1 (the inside

X of a formula is except N-protective group usually used, for example, 2-pilus JINIRU methoxycarbonyl, and 2-KINORI nil carbonyl) sake, According to a process (b) and (d), it is used by whether B exists or it exists as a compound of a formula 4 or a formula 5, respectively.

[0023] If it says more clearly, according to the above-mentioned process (a), the compound of a formula 1 (B does not exist among a formula) can be manufactured by N-alkylation reaction including adding epoxide 2 to the piperidine carboxamide 3. This reaction can be conveniently carried out in the temperature of 20-110 degrees C by putting in the two above-mentioned reacting matter in the state of contact into an inert solvent, for example, ethanol, a tetrahydrofuran, or dimethylformamide. Although reaction time is influenced by temperature and the property of reacting matter, the general range is 2 - 24 hours. When the compound of a formula 1 (B does not exist among a formula) makes the compound with which a formula 4 corresponds, and the reactant derivative of carboxylic-acid X-OH react according to a process (b), it is obtained, respectively. the acid halide which a suitable reactant derivative is the acylating agent which can offer suitable acyl group X-CO, and corresponds -- a chloride or a bromide, activity ester, an anhydride, or the mixed anhydride is included suitably. This reaction is performed according to an approach to have been known for carrying out a reaction including a means to give desired selectivity to reacting matter, and conditions choosing the suitable ratio of reacting matter, or by giving the protective group known by the request for reacting matter besides either which competes with the reaction radical to mean temporarily. Generally, this reaction is performed the reaction time of the range of 15 minutes - 24 hours in the temperature of 0-50 degrees C in an inert solvent, for example, a tetrahydrofuran, dimethylformamide, or methylene dichloride.

[0024] According to the process (c), the compound of a formula 1 (the inside B of a formula is divalent radical-NHCHR5 C(O)- (the inside of a formula and R5 are as the above-mentioned definition)) can be obtained under existence of a coupling agent by carrying out coupling of the compound of a formula 4, and the alpha-amino acid of formula X-NHCHR5 COOH. Using a coupling agent and promoting dehydration coupling of the isolation carboxyl of the reacting matter of 1 and the isolation amino group of other reacting matter is;, for example, the volume ["The Peptides:Analysis, Synthesis, and Biology" / the 1st-8th volume] above-mentioned reference, known well. As an example of a suitable coupling agent, there is a 1 and 1'-carbonyldiimidazole or N, and N'-dichloro hexyl-carbodiimide. As other examples, there is a 1-hydroxy benzotriazol [under existence of N and N-dicyclohexylcarbodiimide] or N-ethyl-N'-[(3-dimethylamino) propyl] carbodiimide. A very practical and useful coupling agent is its tris-(dimethylamino) phosphonium hexafluorophosphate independently available (benzotriazol-1-yloxy) on the commercial target used under existence of 1-hydroxy benzotriazol. other very practical and useful coupling agents -- commercial -- available 2-(1H-benzotriazol-1-IRU)- it is N, N, and N'N'-tetramethyl URONIUMU tetrafluoroborate.

[0025] A coupling reaction is performed in methylene dichloride, an acetonitrile, or an inert solvent like dimethylformamide. Diisopropyl ethylamine or a superfluous organic amine like N-methyl morpholine is added, and a reaction mixture is maintained to abbreviation pH 8. Reaction temperature is usually the range of -20 - 30 degrees C of abbreviation, and reaction time is 8 hours from for 15 minutes. If a process (d) is referred to, this process will be performed by the same approach as the approach described above about the process (b), if it only removes using the compound of a formula 5 instead of the compound of a formula 4 as starting material. The epoxide of the formula 2 used as starting material in a process (a) can be manufactured by the approach which was learned or was learned. If it says in detail especially, the epoxide of a formula 2 can be manufactured by the approach which was indicated by the Europe patent application No. 346,847 by the B.K. pewters of December 20, 1989 issue, or was indicated by above-mentioned patent pending.

[0026] The starting material of others in these processes, i.e., the pyrrolidine carboxamide of a formula 3, and the compound of formulas 4 and 5 are new, therefore are the object of this invention. The suitable approach for manufacture of the compound of formulas 4 and 5 was already explained above. or [that, as for the 3rd kind of a new intermediate product, and the piperidine carboxamide of a formula 3, the many are known] -- or it can be manufactured by choosing suitable 4-permutation piperidine which can be manufactured by the similar approach used for manufacture of known 4-permutation piperidine, and ****** which gives the selected piperidine to an approach to have been known for introducing a carboxamide functional group into the 2nd place of a piperidine. An approach [**** / for permuting the latter] is explained in the following example. The compound of the formula 1 of this invention can be obtained with the gestalt of the acid addition salt which may be permitted in thrapeutics. As an example of such a salt, a salt with a polymer acid, for example, a tannic acid, or a carboxymethyl cellulose and an inorganic acid, for example, halide acid, for example, a hydrochloric acid, a sulfuric acid, or a phosphoric acid is in an organic

acid, for example, an acetic acid, a lactic acid, a succinic acid, a benzoic acid, a salicylic acid, methansulfonic acid or p-toluenesulfonic acid, and a list. It converts into the salt which may be permitted pharmacologically [other acid addition salts, for example, avirulent,] in a specific acid addition salt by processing with suitable ion exchange resin by "Helv.Chim.Acta" by R.A. BOISONASU and others, and the approach indicated by 43 and 1849 (1960) by request. Generally, the salt which may be permitted like thrapeutics of the peptide of a formula 1 is biologically [as the peptide itself] equal enough.

[0027] The cell protective effect over the HIV protease inhibition property and HIV pathogen of the compound of the biological viewpoint type 1 or its salt which may be permitted in thrapeutics can be proved by biochemical, microbiological, and the biological method. Especially the effective approach for proving the compound of a formula 1 or its HIV protease inhibition property of a salt which may be permitted in thrapeutics is "recombinant HIV protease HPLC assay." ;H.G. clough SURIHHI et al. and the "Proc.Nat.Acad.Sci.USA" 86,807 (1989) reference based on the capacity for a trial compound to check enzyme division by the HIV protease of the deca peptide (substrate) which has the amino acid sequence in which this approach includes the HIV protease division part where HIV polyprotein was known. The result obtained with the instantiation compound of the detail about this assay and a formula 1 is indicated in the following example. The capacity for the compound of a formula 1 and its salt which may be permitted in thrapeutics to protect a cell from HIV infection can be proved by the microbiological approach of evaluating the inhibition effectiveness of a trial compound over cytopathogenic [of HIV of Homo sapiens T-four cellular in]. Such an example of a type of an approach is indicated by "Science" by "Jpn.J.Cancer Res. (Gann)" by S. Harada and N. Yamamoto, 76,543 (1985), and S. Harada and others, and 229 and 563 (1985). The assay based on the latter approach is indicated in the following example.

[0028] When the compound of this invention or its salt which may be permitted in thrapeutics is used in order to repulse a human HIV infectious disease, a medicine can be prescribed for the patient taking-orally-wise [this peptide] as an excipient containing 1 or the support beyond it which may be permitted pharmacologically, locally, or parenterally, and that rate is determined by the solubility, the chemical property, the selected route of administration, and standard biological custom of that compound. For internal use, said compound or its salt which may be permitted in thrapeutics can be prescribed by the capsule containing the active ingredient of the amount at which the range of about 5-150mg was beforehand appointed into the support which may be permitted pharmacologically, respectively, or unit administration gestalt object like a tablet. Said compound can be prescribed by the excipient which contains an activator 0.05 to 1% preferably 0.01 to 2% and which may be permitted pharmacologically for partial administration. these formula objects -- a cream, a lotion, and a sublingual tablet -- or it can consider as the gestalt of an endermic patch or a cheek patch preferably. For parenteral administration, the compound of a formula 1 is prescribed for the patient hypodermically or by carrying out an intramuscular injection in a vein as a constituent with the excipient or support which may be permitted pharmacologically. For administration by injection, it is desirable to use it in the solution in the sterilized water nature excipient which can also contain the solute of others like a buffer or a preservative enough besides the salt which may be permitted pharmacologically or glucose of an amount, in order to make a solution isosmotic for said compound. The suitable excipient or the support for the above-mentioned formula object is indicated in a standard pharmaceutical-sciences textbook, for example, "Remington's Pharmaceutical Sciences", the 18th edition, a Mac publishing company, U.S. Pennsylvania Easton, and 1990.

[0029] The dose of a compound changes with an administration gestalt object and the specific selected activators. Furthermore, it changes with the specific hosts under a therapy. Generally, a therapy is started by the small few dose more substantially than the optimal dose of a peptide. Then, it is increased by the dose by increasing little by little until the optimal effectiveness is acquired under the environment. Generally, as for this compound, it is most desirable to prescribe a medicine for the patient in the concentration criteria which generally acquire anti-viral effectiveness, without causing any harmful side effects harmful to ****** again. an internal use sake -- this compound or its salt which may be permitted in thrapeutics -- the weight per day of 1kg -- the range of 0.5-15mg -- a medicine is preferably prescribed for the patient in 0.5-5mg about the weight of 1kg. Although the compound of a formula 1 also has the above-mentioned variate in relation to generalized administration, it is 1micro per weight of 1kg g-100microg. A medicine is prescribed for the patient with a dose. Although the formula object indicated above is the effective and comparatively safe physic for the therapy of a HIV infectious disease, such formula object and other anti-viral physic, or possible collaboration administration with ** is not eliminated. Such other anti-viral physic or ** includes fusibility CD 4, zidovudine, didanosine, zalcitabine, phosphono formate 3 sodium, RIBABARIN, aciclovir, or anti-viral interferon (for example, alpha-interferon or interleukin-2).

[0030]
[Example] Hereafter, an example explains this invention in more detail. Especially the percentage or ratio of a solution shows the relation of capacity pair capacity, unless it refuses. Temperature is shown by Centigrade. a proton nuclear-magnetic-resonance (NMR) spectrum -- Bruker 200MHz; recorded on the spectrometer -- a chemical deviation (delta) -- ppm It is reported. The abbreviation used into the example Boc : tert - Butyloxy carbonyl; [BOP] : Tris (Benzotriazol-1-yloxy) Phosphonium hexafluorophosphate; (Dimethylamino) But : tert- Butyl; Bzl : benzyl; -- DIEA:diisopropyl ethylamine; -- DMF : Dimethylformamide; HEPES:N-2-hydroxyethyl piperazine-N'-2-ethane-sulfonic-acid;Et2O: -- diethylether;EtOAc: -- ethyl-acetate;EtOH: -- ethanol;HPLC: -- high-performance-liquid-chromatography;MeOH: -- methanol ;P h:phenyl; -- THF : Tetrahydrofuran;Z : include benzyloxycarbonyl.
[0031] The solution of 1-(tert-butyloxy carbonyl)-4-PIPERIJI Norian (3.0g, 14.9mmol) was cooled at 0 degree C during the manufacture THF (30ml) of an example 11-(tert-butyloxy carbonyl)-4-(phenylthio) piperidine. Triethylamine (3.2ml, 1.5Eq) was added in this solution, and, subsequently the methyl-chloride sulfonyl (1.26ml, 1.1Eq) was added gradually. This reaction mixture was agitated in 0 degree C for 2 hours. Et2O (30ml) and H2O (20ml) were added, and the obtained mixture was agitated for 30 more minutes in 0 degree C. This mixture was diluted by Et2O (200ml). H2O, 10% aquosity citric acid, the saturated water solution (2X) of NaHCO3, and brine washed the organic layer continuously. Vacuum concentration of the organic layer was dried and (MgSO4) carried out, and 1-(tert-butyloxy carbonyl)-4-piperidino RUMECHIRU-sulfonate ester (4.0g, 96%) was obtained as a solid which wore the yellow taste. 1NMR (CDCl3) delta4.90 (m, 1H), 3.72 (ddd, J= 4.3, 6.5 or 13.5Hz, 2H), 3.32 (ddd, J= 4.3, 8.1 or 13.5Hz, 2H), 3.05 (s, 3H), 1.47 (s, 9H).
[0032] It was used without refining the above-mentioned methylsulfonate further, and :thiophenol (1.84ml, 17.9mmol) which manufactured the compound of a mark as follows was slowly added in 0 degree C to the suspension of NaF (334mg, 14.3mmol) in DMF (8ml). The solution of above-mentioned methyl SUHONETO (2.0g, 7.17mmol) in DMF (6ml) was added, and the obtained mixture was agitated in the room temperature for 18 (20-22 degrees C) hours. This mixture was diluted by Et2O and the aquosity NaOH of 1M (3X) and brine washed the organic layer continuously. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (it is [SiO2, an eluate:EtOAc-hexane, 1:9, and] 1:6 behind) refined survival, and that the mark compound could be made into oily matter (1.82g, 86%), when it was left, it solidified. 1HNMR(CDCl3) delta7.48-7.2 (2m, 2H+3H), 3.97 (m, 2H), 3.22 (m, 1H), 2.80 (ddd, J= 3.8, 10.5 or 13.5Hz, 2H), 1.47 (S, 9H). A FAB mass spectrum, m/z:294(M+H)+.
[0033] The solution of the mark compound (3.57g, 12.2mmol) of 2d of examples and the example 1 in manufacture Et2O (60ml) of the l-cis--N-tert-butyl-1-(tert-butyloxy carbonyl)-4-(phenylthio) piperidine-2-carboxamide was cooled at -78 degrees C. The N, N, N', and N'-tetramethylenediamine (4.6ml, 2.5Eq) was added in the solution which the above cooled, and, subsequently the 1.3Msec(s)-butyl lithium in a chloro hexane (12.0ml, 1.3Eq) was added gradually. This mixture was agitated in -78 degrees C for 3.5 hours. then, tert-butyl isocyanate (2.1ml, 1.5Eq) -- base -- it added quickly and the obtained reaction mixture was agitated for 40 minutes in -78 degrees C. This reaction mixture was quenched by the aquosity citric acid 10%, and, subsequently was made to warm to a room temperature. The organic layer was separated and Et2O extracted the virus for aquosity. The saturated water solution and brine of NaHCO3 wash the doubled organic layer, and it dried (MgSO4) and was made to evaporate under reduced pressure. Although flash chromatography (SiO2, an eluate: hexane-EtOAc, 6:1, and after that 4:1) refined survival and the mark compound was obtained as colorless oily matter (4.34g, 90%), it was solidified by leaving it. 1HNMR (CDCl3) delta -- 7.42 (m, 2H) and 7.28 (m --) 3H, 5.85 (double width s, 1H), and 4.43 (dd and J= -- 4.0 or 7.0Hz) 1H, 3.92 (ddd, J= 3.5, 5.0 or 13.5Hz, 1H), 3.49 (m, 1H), 3.32 (ddd, J= 4.0, 11.5 or 13.5Hz, 1H), 1.48 (s, 9H), 1.39 (s, 9H). A FAB mass spectrum, m/z:393(M+H)+.
[0034] The solution of 1-(tert-butyloxy carbonyl)-4-PIPERIJI Norian (5.2g, 25.9mmol) under manufacture DMF (20ml) of 3d of examples and the l-cis--N-tert-butyl-1-(tert-butyloxy carbonyl)-4-(2-piperidinyloxy) piperidine-2-carboxamide, tert-butyldimethylsilyl chloride (4.07g, 1.05Eq), and an imidazole (2.7g, 1.5Eq) was agitated for 16 hours. After diluting by Et2O, H2O (2X), 10% aquosity citric acid, the saturated water solution of NaHCO3, and brine washed this solution continuously. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out. survival -- WATERS(trademark) LC-500 preparative-chromatography equipment [2SiO2 column: -- HPLC which uses hexane-EtOAc (19:1), Millipore Corporation, and U.S. Massachusetts Milford] refined, and the 1-(tert-butyloxy carbonyl)-4-(tert-butyldimethylsiloxy) piperidine (7.54g, 92%) was obtained. 1HNMR(CDCl3) delta3.87 (m, 1H), 3.61 (ddd,

J= 3.5, 7.5 or 13.0Hz, 2H), 3.24 (ddd, J= 3.7, 8.0 or 13.0Hz, 2H), 1.48 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H). Then, according to the procedure of an example 2, d and the l-cis--N-tert-butyl-1-(tert-butyloxy carbonyl)-4-(tert-butyldimethylsiloxy) piperidine-2-carboxamide were obtained instead of the 1-(tert-butyloxy carbonyl)-4-(phenylthio) piperidine except using the above-mentioned 1-(tert-butyloxy carbonyl)-4-(tert-butyldimethylsiloxy) piperidine. 1HNMR(CDCl3) delta5.70 (s, 1H), 4.47 (dd, J = 2.7 or 8.0Hz, 1H), 4.07 (m, 1H), 3.83 (m, 1H), 3.22 (ddd, J= 5.4, 10.5 or 13.5Hz), 1, 48 (s, 9H), 1.35 (s, 9H), 0.88 (s, 9H), 0.1 and 0.08 (2s, 6H).

[0035] To the solution of the above-mentioned compound (700mg, 1.69mmol) in THF (10ml), the solution of 1M tetrabutylammonium fluoride in THF (2.15ml, 1.25Eq) was added. This reaction mixture was agitated for 30 minutes in the room temperature, and, subsequently it diluted by Et2O. H2O (2X) and brine (1X) washed the obtained mixture. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 1:1) refined survival, and the carboxamide, d, and the l-cis--N-tert-1-(tert-butyloxy carbonyl)-4-hydroxy piperidine-2-carboxamide (386mg, 76%) were obtained as a white solid. A FAB mass spectrum, m/z:301(M+H)+. The diethyl azo dicarboxy rate (173microl, 1.5Eq) was added in the above-mentioned carboxamide (220mg, 0.73mmol) in benzene-THF (5:1 or 13ml), 4-nitro benzoic acid (244mg, 2.0Eq), and the cold solution (0 degree C) of triphenyl phosphine (288mg, 1.5Eq). The reaction mixture was agitated in the room temperature for 30 minutes for 3 hours in 0 degree C after that. The solvent was removed under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAC, 4:1) refined survival, and d containing about 25 - 30% of contamination (discharge product) and the l-trans-N-tert-butyl-1-(butyloxy carbonyl)-4-(4-nitrobenzoyloxy)-2-carboxamide (280mg) were obtained. It was used in the following process, without refining all products further.

[0036] The product (404mg, 0.9mmol) of the latter in MeOH (9ml) and the mixture of K2 CO3 (mg [28], 0.2Eq) were agitated in the room temperature for 18 hours. The solvent was removed under reduced pressure. It is survival CHCl3 It is H2O about the solution which dissolved in inside and was obtained. It washed, and it dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 1:1, and after that 1:2) refined survival, and d and the l-trans-tert-butyl-1-(N-tert-butyloxy carbonyl)-4-hydroxy piperidine-2-carboxamide (194mg, 71%) were obtained. The solution of the compound (145mg, 0.48mmol) of the latter in benzene-THF (5:1 or 12ml), 2-hydroxypyridine (68mg, 1.5Eq), and triphenyl phosphine (187mg, 1.5Eq) was cooled at 0 degree C. The diethyl azo dicarboxy rate (114microl, 1.5Eq) was added in this solution. This mixture was agitated for 30 minutes in the room temperature for 1.5 hours in 0 degree C after that. The solvent was removed under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 2:1) refined survival, and the mark compound of this example was obtained (70mg, 38%). 1NMR(CDCl3) delta8.12, 7.43 and 6.85, and 6.62 (4m, 4H), 5.72 (s, 1H), 5.39 (m, 1H), 4.63 (m, 1H), 4.05 (m, 1H), 3.29 (m, 1H), 1.48 (s, 9H), 1.36 (s, 9H).

[0037] The mark compound (1.68g, 4.28mmol) of 4d of examples and the example 2 in manufacture CH2Cl2 (20ml) of the l-cis--N-tert-butyl-1-(tert-butyloxy carbonyl)-4-(phenyl sulfonyl) piperidine-2-carboxamide and the mixture of 3-chloro peroxybenzoic acid (2.2g, 12.83mmol) were agitated in the room temperature for 18 hours. The obtained reaction mixture was quenched with 10% aquosity solution of a sodium sulfite, and, subsequently was diluted by EtOAc. An organic layer is separated and they are the saturated water nature solution of NaHCO3, and H2O. And brine washed continuously, and it dried (MgSO4) and condensed under reduced pressure. Solid survival was ground by hexane-EtOAc (18ml / 12ml), subsequently it collected on the filter paper, and the mark compound was obtained as a white solid (1.57g, 86%). 1.45 (s, 9H) 1NMR(CDCl3) delta7.90 (m, 2H), 7.75-7.55 (m, 3H), 5.95 (s, 1H), 4.07 (dd, J = 8.0 or 9.5Hz, 1H) and 3.88 (dt, J = 5.4 or 13.5Hz, 1H), 3.32-3.05 (m, 2H), 1.35 (s, 9H). A FAB mass spectrum, m/z:425(M+H)+. Except using 3-chloro peroxybenzoic acid of only the one-mol equivalent, d and the l-cis--N-tert-butyl-1-(tert-butyloxy carbonyl)-4-(phenyl sulfinyl) piperidine-2-carboxamide were obtained according to the procedure of this example.

[0038] example 5 N-tert-butyl -1 -- the - [3(S)-(tert-butyloxy carbonylamino)-2(R)-hydroxy-4-phenyl butyl]-4(R)-(phenylthio) piperidine-2(S)-carboxamide (R1=H in which formula 1;X=Boc and B do not exist --) R2 =C3 (CH3) And the manufacture (a) d of Y=PhS, l-cis--N-tert-butyl-4-(phenylthio) piperidine-2-carboxamide, The inside of :6NHCl / dioxane which manufactured the piperidine carboxamide of a formula 3 (C [3] (CH3) and Y of the inside of a formula and R2 are PhS(s)) as follows, Boc to which the piperidine carboxamide corresponds In a room temperature, agitate the protected derivative (3.04g, 7.76mmol), i.e., the mark compound of an example 2, for 20 minutes, and, subsequently to the bottom of reduced pressure,

concentration hardening by drying is carried out. The piperidine carboxamide of a request of a formula 3 (Y is among a formula and R2 is PhS in C (CH3)3) was obtained.
(b) The piperidine carboxamide of the latter in :EtOAc (50ml) which manufactured the mark compound of this example as follows, and the mixture of the 2-N aquosity NaOH (20ml) were agitated for 15 minutes in the room temperature. An organic layer is separated and it is H2O of the minimal dose. And brine washed, it dried (MgSO4) and evaporation to dryness was carried out under reduced pressure. The obtained oily matter was dried for about 45 minutes under the high vacuum. This oily matter was mixed with epoxide [of a formula 2], 3(S)-(tert-butyloxy carbonylamino)-1, and 2(R)-epoxy-4-phenyl butane (2.45g, 9.36mmol) (refer to [above-mentioned / B.K. pewter]), and anhydrous [EtOH] (40ml). This mixture was heated under reflux for 18 hours. After adding the epoxide (600mg) of the amount of additions, this mixture was heated under reflux for 4 hours. Concentration hardening by drying of this mixture was carried out under reduced pressure. It is 34%] to the isomer (polarity) of [1.46g and the request which refined the rough product by HPLC which uses WATERS(trademark) LC-500 preparative-chromatography equipment [2SiO2 column:hexane-EtOAc (6:4), Millipore Corporation, and U.S. Massachusetts Milford], and obtained the mark compound as a white foamy object. A FAB mass spectrum, m/z:556(M+H)+.
[0039] According to the procedure of an example 5, the compound of others of a formula 1 (B does not exist among a formula but X, R1, R2, and Y are as the above-mentioned definition) can be manufactured. For example Equivalent 3(S)-(tert-butyloxy carbonylamino)-1 and 2(R)-epoxy-4-(4-fluoro phenyl) butane instead of 3(S)-(tert-butyloxy-carbonylamino)-1 and 2(R)-epoxy-4-phenyl butane By using it N-tert - butyl - one - {-- three -- (-- S --) - {(benzyloxycarbonyl) -- amino --} - two -- (-- R --) - hydroxy ones - four - (4-fluoro phenyl) -- butyl --} -4 (R) - (phenylthio) - a piperidine-2(S)-carboxamide [FAB mass spectrum -- m/z: 608(M+H)+] is obtained. The example of others of such a compound is shown in Table I. the equivalent epoxide of a formula 2 which these examples are alike, respectively, sets and is shown in front Naka instead of the epoxide of the formula 2 given in an example 5 -- moreover, the equivalent piperidine carboxamide of the formula 3 shown in front Naka instead of the piperidine carboxamide of the formula 3 given in an example 5 is used.
[0040]
[Table 1]
Table I number A formula 2 Piperidine of a formula 3 Product : [N-tert-butyl-1-] epoxide Carboxamide 3 (S)-{(X)-amino} - {-- 2(R)-hydroxy-4-phenyl - Butyl}-Y-piperidine -2 (S) - The carboxamide X R1 R2 Y X//Y 1 Z H But Ph Benzyloxycarbonyl// 4- (R)-phenyl (558) * 2 Z H But Bzl Benzyloxycarbonyl// 4- (R)-benzyl (572)
3 Z H But So2Ph Benzyloxycarbonyl// 4- (R) - (Phenyl Sulfonyl)
(662)
4 Z H But SPh Benzyloxycarbonyl// 4- (R) - (Phenylthio) (590)
5 Z H But OPh Benzyloxycarbonyl// 4- (R)-Phenoxy (574)
6 Z H But O- (2- Benzyloxycarbonyl// 4- Pyridyl) (R) - (2-Pilus JINIRU Oxy-)
(575)
7 Z H But SHIKUROHE Benzyloxycarbonyl// 4- KISHIRU (R)-Cyclohexyl (564)
8 Z H But S- (2- Benzyloxycarbonyl// 4- Pilus JINIRU) (R) - (2-PIRIJI Nil Thio)
(591)
9 Z H But S- (4- Benzyloxycarbonyl// 4- Pilus JINIRU) (R) - (4-PIRIJI Nil Thio)
(591)
10 Z H But S- (2- Benzyloxycarbonyl// 4- Pyrimidinyl) (R) - (2-Pyrimidinyl Thio)
(592)
11 Z H But S - (4 6- Benzyloxycarbonyl//4- Dimethyl-2- (R)-(4, 6-Dimethyl-2- Pyrimidinyl) Pyrimidinyl Thio) (620)
12 Z H But SCH2Ph Benzyloxycarbonyl// 4- (R)-Benzyl Thio (604)
13 Z H But S-(4- Benzyloxycarbonyl//4- Pilus JINIRU- (R)-{(4-Pilus JINIRU Methyl)- Methyl) Thio}
(605)
14 Z H But S-(3- Benzyloxycarbonyl//4- Pilus JINIRU- (R)-{(3-Pilus JINIRU Methyl)- Methyl) Thio}
(605)
15 Boc H O But - (2- Tert- [Butyloxy Carbonyl// 4- Pilus JINIRU-] (R)- (2-Pilus JINIRU Methoxy)) Methyl (555)
16 Boc H But S-(2- Tert-Butyloxy Carbonyl//4- Pilus JINIRU- (R)-{(2-Pilus JINIRU Methyl)- Methyl) Thio} (571)

17 Boc H But O- (2- Tert-Butyloxy Carbonyl//4- Pyrimidinyl) (R) - (2-Pyrimidinyl Oxy-) Methyl (542)
18 Boc H But O-(4 6- Tert-Butyloxy Carbonyl//4- Dimethyl-2- (R)-{(4, 6-Dimethyl-2- Pyrimidinyl) Pyrimidinyl) Oxy-} (570)
19 Boc H But O-(4-Methyl- Tert-Butyloxy Carbonyl//4- 2-Pyrimidinyl) (R)-{(4-Methyl-2- Pyrimidinyl) Oxy-} (556)
20 Boc H But O-(2 6- Tert-Butyloxy Carbonyl//4- Dimethyl-4- (R)-{(2, 6-Dimethyl -4 - Pyrimidinyl) Pyrimidinyl) Oxy-} (570)
21 Boc H But S -(2 6- Tert-Butyloxy Carbonyl//4- Dimethyl-4- (R)-{(2, 6-Dimethyl-4- Pyrimidinyl) Pyrimidinyl)- Thio} (586)
22 Boc H But S-(4- Tert-Butyloxy Carbonyl//4- Methyl-2- (R)-{(4-Methyl-2- Pyrimidinyl) Pyrimidinyl) Thio} (572)
----------* -- observation (M+H) + by which the numeric value in the parenthesis after the name of each product was acquired from the FAB mass spectrum of the product it is .
[0041] Two approaches for manufacture of the compound of example 6 formula 1 (the inside of a formula and B are divalent radical-NHCHR5 C(O)- (the inside R5 of a formula is as the above-mentioned definition)) are offered in this example. The 1st instantiation approach and example 6A are suitable for the compound of a formula 1 (the inside of a formula and B are Asn it is except), and the 2nd instantiation approach and example 6B are suitable for the compound of a formula 1 (the inside of a formula and B are Asn(s)). A: N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (tert-butyloxy carbonyl) -- the valyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide (formula 1; X= it Boc(s)) B=Val, R1 =H, and R2 =C (CH3)3 and the formula 1 (among a formula) in manufacture 6NHCl / dioxane of Y=PhS (10ml) X -- Boc it is -- B - - not existing -- R1 =H and R2 =C (CH3)3 And compound (1.14g, 2.04mmol) of Y=PhS, That is, the solution of the mark compound of an example 5 was agitated for 20 minutes in the room temperature. The solvent was removed under reduced pressure. White solid survival was ground by Et2O, it collected on the filter paper, and it was made to dry and the corresponding amine by which deprotection was carried out was obtained as a hydrochloride (1.06g, 98%).
[0042] The latter compound (341mg and 0.645mmol) was dissolved into CH2Cl2 (3.5ml). DIEA (225microl, 1.29mmol), protected amino acid Boc-Val-OH (145mg and 0.667mmol), and BOP (342mg and 0.774mmol) were added in the above-mentioned salting in liquid. This reaction mixture is set to a room temperature, and it is 3.5. pH was maintained to 8 by inspecting periodically and adding DIEA if needed, carrying out time amount churning. Then, it is EtOAc about this reaction mixture. It dilutes and they are the saturated water solution (2X) of NaHCO3, and H2O. And brine washed continuously. This organic layer was dried (MgSO4) and it condensed under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 1:1) refined the obtained survival, and the mark compound of the section A of this example was obtained as a white solid (338mg, 80%). A FAB mass spectrum and m/z:655.3+ (M+H).
B: N-tert - butyl - one - {-- three -- (-- S --) - {-- {-- N - (tert-butyloxy carbonyl) -- the asparaginyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide (formula 1; X=Boc) B=Asn, R1 =H, and R2 =C3 (CH3) And manufacture of Y=PhS [0043] 1-hydroxy benzotriazol (1.97g and 14.57mmol) was added to the solution (0 degree C) with which N and N'-dicyclohexylcarbodiimide (2.4mmol in CH2Cl2 / ml, 6.7ml, and 16.08mmol) and THF (45ml) were cooled. This mixture was agitated for 15 minutes. The solution of the amine (3.30g, 7.24mmol) by which deprotection was carried out with which the mark compound of the example 5 in protected amino acid Boc-Asn-OH (3.38g and 14.57mmol) and DMF (40ml) corresponds was added to this mixture. (Cautions: This amine by which deprotection was carried out was obtained by changing that hydrochloride into that free base after that by the approach given in the 1st paragraph of example 6A.) To the room temperature, this mixture was warmed slowly and, subsequently was agitated for 18 hours. Then, it is EtOAc about this mixture. And it diluted by H2O. An organic layer is separated and they are the saturated water solution of NaHCO3, and H2O. And brine washed, it dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, eluate:CHCl3-MeOH, and 97.5:2.5) refined solid survival, and the mark compound of the section B of this example was obtained as a white solid (3.56g, 73%). A FAB mass spectrum and m/z:670(M+H)+.
[0044] According to the procedure of an example 6, the compound of others of a formula 1 (B is divalent radical-NHCHR5 C(O)- among a formula (the inside of a formula and R5 are as the above-mentioned definition), and R1, R2, and X and Y are as the above-mentioned definition) can be manufactured. It is

related with the section A of this example. For example, instead of the mark compound of an example 5 an example -- five -- indicating -- having had -- etc. -- an amount -- N-tert - butyl - one - {-- three -- (-- S --) - {(benzyloxycarbonyl) -- amino --} - two -- (-- R --) - hydroxy one - four - (4-fluoro phenyl) -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide -- By using it N-tert-butyl - 1-{3(S)-{{N-(benzyloxycarbonyl) valyl} amino}-2(R)-hydroxy-4-(4-fluoro phenyl) butyl --} -- a -4(R)-(phenylthio) piperidine-2(S)-carboxamide {mass spectrum -- m/z: 707(M+H)+} is obtained. The example of others of these compounds is shown in Table II. The formula 1 (among a formula) indicated by the example 6 in each of these examples Instead of the compound not existing, B is the formula 1 (among a formula) shown in front Naka of the equivalent. the starting material with which B does not exist -- using it --; (when it differs) -- again instead of the amino acid from which the publication in the example 6 was protected The amino acid from which formula PG-AA-OH (PG is an alpha-amino-acid protective group among a formula, and AA is the amino acid residue of formula NHCHR5 C (O) and (the inside of a formula and R5 being as the above-mentioned definition)) of the equivalent indicated in Table II was protected is used.

[0045]

[Table 2]

Table II number Inside of Table I of an example 6 Formula PG-AA-OH Product : [N-tert-butyl-1-] Starting material of a formula 1 It was protected. {3(S)-{{N-PG- A number Amino acid AA} amino}-2(R)-Hydroxy-4-phenyl - Butyl}-Y-piperidine - The 2(S)-carboxamide ---------- PG AA PG-AA//Y ---------- 1 1 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - () [phenyl-] Thio (689) * 2 1 Z Asn (benzyloxycarbonyl) - Asparaginyl//4(R)- (phenylthio) (704.3)
3 1 Boc Asn (Tert-Butyloxy KARUBO- Nil) Asparaginyl// 4 (R) - (Phenylthio)
(670)
4 2 Z Val (Benzyloxycarbonyl) - Valyl// 4(R)-Phenyl (657)
5 2 Z Ile (Benzyloxycarbonyl) - Isoleucyl//4(R)- Phenyl (671)
6 2 Z Asn (Benzyloxycarbonyl) - Asparaginyl//4(R)- Phenyl (672)
7 3 Z Val (Benzyloxycarbonyl) - Valyl// 4(R)-Benzyl (671)
8 4 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (Phenyl- Sulfonyl) (721)
9 4 Z Asn (Benzyloxycarbonyl) - Asparaginyl//4(R)- (Phenyl Sulfonyl)
(736)
10 5 Z Val (Benzyloxycarbonyl) - Valyl// 4(R)-Phenoxy (673)
11 5 Z Asn (Benzyloxycarbonyl) - Asparaginyl//4(R)- Phenoxy (688)
12 6 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (2- Pilus JINIRU Oxy-) (674)
13 7 Z Val (Benzyloxycarbonyl) - Valyl//4(R)- Cyclohexyl (663)
14 8 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (2- PIRIJI Nil Thio) (690)
15 9 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (4- PIRIJI Nil Thio) (690)
16 10 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (2- Pyrimidinyl Thio) (691)
17 11 Z Val (Benzyloxycarbonyl) - Valyl//4(R)-{(4, 6- Dimethyl-2-Pyrimidinyl)- Thio} (719)
18 12 Z Val (Benzyloxycarbonyl) - Valyl//4 (R) - (Benzyl- Thio) (703)
19 13 Z Val (Benzyloxycarbonyl) - Valyl//4(R)-{(4- Pilus JINIRU Methyl) Thio}
(704)
20 14 Z Val (Benzyloxycarbonyl) - Valyl//4(R)-{(3- Pilus JINIRU Methyl) Thio}
(704)
21 16 Z Val (Benzyloxycarbonyl) - Valyl//4(R)-{2- Pilus JINIRU Methyl Thio}
(704)
* observation (M+H) + by which the numeric value in the parenthesis after the name of each product was acquired from the FAB mass spectrum of a product it is .

[0046] Example 7 N-tert-butyl-1-{2 (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the valyl --} -- amino --} - butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide (formula 2;X=2-KINORI nil carbonyl, B=Val, and R1 =H --) R2 =C3 (CH3) And the solution of the mark compound (167mg and 0.255mmol) of the section A of the example 6 in manufacture 6NHCl / dioxane of Y=PhS (2.0ml) was agitated for 20 minutes in the room temperature. The solvent was removed under reduced pressure. The survival of a white solid was dried for 20 minutes under the high vacuum, and the corresponding amine by which deprotection was carried out was obtained as a hydrochloride. This salt was dissolved into CH2Cl2 (2ml). DIEA (89microl and 0.510mmol), 2-quinoline carboxylic acid (48.6mg and 0.280mmol), and BOP (135mg and 0.306mmol) were added in the solution of said salt. This mixture is set to a room temperature, maintaining pH of this reaction mixture to 8 by

inspecting periodically and adding DIEA if needed, and it is 3.5. Time amount churning was carried out. Then, it is EtOAc about this reaction mixture. It diluted and the saturated water solution (2X) of NaHCO3, H2O, and (2X) brine washed continuously. The organic layer was dried (MgSO4) and concentration hardening by drying was carried out under reduced pressure. Flash chromatography (SiO2, an eluate: hexane-EtOAc, 2:3) refined the obtained colorless oily matter, and the mark compound was obtained as a white solid (161mg, 89%). A FAB mass spectrum, m/Z:710(M+H)+. Although the procedure of the section B of an example 6 is followed when the procedure of an example 7 or starting material is the compound of a formula 1 (the inside of a formula and B are Asn(s)) Respectively instead of the compound of the section A of an example 6, or the mark compound of an example 5 Formula 1 (the inside of a formula and B being divalent radical-NHCHR5 C(O)- (among a formula)) R5 it is as the above-mentioned definition -- the radical list for which X is usually used and of which N-protection was done -- R1 -- R2 Y uses the suitable compound of being as the above-mentioned definition. And again If the suitable carboxylic acid of formula X-OH (the inside of a formula and X are as the above-mentioned definition) is used instead of 2-quinoline carboxylic acid or amino acid Boc-Asn-OH (in the case of the section B of an example 6) by which deprotection was carried out, respectively The following compound of a formula 1 shown in Table III is obtained.

[0047]

[Table 3]

Table III number Product : [N-tert-butyl-1-{3(S)-{N-{PG-AA}-] Amino}-2(R)-hydroxy-4-phenyl butyl}-Y- The piperidine-2(S)-carboxamide ---------- PG-AA//Y ----------

- 1 (2-KINORI nil carbonyl) Asparaginyl//4(R)- Phenoxy (709) * 2 (2-KINORI nil carbonyl) Asparaginyl//4 (R)- (phenyl sulfonyl) (757)

3 2-KINORI Nil Carbonyl Asparaginyl//4(R)- (Phenylthio) (725)

4 2-North America Free Trade Agreement RENIRU Carbonyl Valyl//4(R)- (Phenylthio) (709)

5 2-North America Free Trade Agreement RENIRU carbonyl asparaginyl//4(R)- (phenylthio) (724) * the numeric value in the parenthesis after the name of each product -- observation [of the mass spectrum of a product] (M+H) + it is .

[0048] Example 8 N-tert-butyl-1-{2 (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - {(2-pilus JINIRU methoxy) -- carbonyl --} -- the isoleucyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenyl -- a piperidine - two -- (-- S --) - the carboxamide (B=Ile formula 1;X=2-pilus JINIRU methoxycarbonyl --) R1 =H, R2 =C3 (CH3) And Y=PhS Manufacture N-tert-butyl-1-{3 (S) - amino -2 (R) - hydroxy-4-phenyl butyl}-4 (R) - phenyl piperidine -2 (S) - carboxamide -- {N-tert-butyl-1-{3(S)-(benzyloxycarbonylamino)-2(R)-hydroxy-4-phenyl butyl}-4(R)-phenyl piperidine-2(S)-carboxamide (compound 1 reference of Table I) 0.605mg -- } manufactured by the hydrogenolysis (5%Pd/C, MeOH1 atmospheric pressure, 2 hours) of (0.108mmol) was dissolved into DMF (1.6ml). Lithium salt [of N-{(2-pilus JINIRU methoxy) carbonyl} isoleucine] (32mg and 0.228mmol), 1-hydroxy benzotriazol (32mg and 0.237mmol), and N-ethyl-N'-{3-(dimethylamino) propyl} carbodiimide (45.4mg and 0.237mmol) was added in this solution. This mixture was agitated in the room temperature for 18 hours. Then, this reaction mixture was diluted by Et2O, the saturated water solution (2X) and brine of H2O and NaHCO3 washed, and evaporation to dryness was dried and (MgSO4) carried out. Flash chromatography (SiO2, eluate:CHCl3, MeOH, 97.5:2.5, and after that 95:5) refined the oily matter of the obtained yellow, and the mark compound was obtained as a white solid (58.7mg). A FAB mass spectrum and m/z:672(M+H)+.

[0049] Example 9 N-tert-butyl-1-{2 (-- R --) - hydroxy one - three -- (-- S --) - {-- N - {-- {-- N - methyl - N - (2-pilus JINIRU methyl) -- amino --} -- carbonyl --} - the valyl --} - four - phenyl -- butyl --} - four -- (-- R --) - (phenylthio) -- a piperidine - two -- (-- S --) - the carboxamide (formula 1;X=R3 NR4 C (O) (among a formula)) R3 = (2-pilus JINIRU methyl) and R4 =CH3, and B=Val, R1 =H and R2 =C3 (CH3) And the solution of the 1.9 M phosgene of the manufacture toluene (9.41ml and 17.89mmol) of Y=PhS was added to the suspension of H-Val-OCH3 and HCl (1.0 g, 5.96mmol). Reflux heating of this reaction mixture is carried out under dry ice condensing plant for 2 hours, and it cools to a room temperature, and is nitrogen 1.5 It sprinkled violently time and, subsequently concentration hardening by drying was carried out. Toluene (5ml) was added to survival, concentration hardening by drying of the obtained solution was carried out, and (S)-2-isocyanate-3-methyl butanoic acid methyl ester was obtained. Under the high vacuum, it dried for 5 minutes and, subsequently this product was used in the following process. 1 NMR(CDCl3) delta3.95- 3.94 (d, J= 3.82Hz, 1H), 3.81 (s, 3H), 2.35-2.22 (m, 1H), 1.04-1.02 (d, J= 6.8Hz, 3H), and 0.91-0.89 (d, J= 6.74Hz, 3H).

[0050] The top Norio product (471mg, 3.00mmol) was dissolved into toluene (5ml). Written} was added in

this solution N-methyl-N-(2-pilus JINIRU methyl) amine {336mg, 3.00mmol(s), A. Fischer, "Can.J.Chem.", and 56 and 3059 (1978). It is the obtained mixture N2 In 90 degrees C, it agitated in the bottom for 16 hours. The solvent was evaporated, flash chromatography (SiO2, eluate:EtOAc-MeOH, 24:1) refined survival, and N-{{N-methyl-N-(2-pilus JINIRU methyl)-amino} Carbonyl} valine} methyl ester (616mg, 73%) was obtained as orange oily matter. 1 NMR(CDCl3) Delta8.58-8.55 (D, 1H) and 7.72-7.65 (T --) 1H, 7.29-7.19 (m, 2H), 6.20-6.05 (double width s, 1H), and 4.55 (s, 2H) and 4.45 -4.40 (m, 1H), 3.71 (s, 3H) and 3.04 (s, 3H), 2.21-2.12 (m, 1H), and 1.0-0.92 (dd, 6H). About the solution of 1NLiOH (1.72ml;1.72mmol), they are dioxane (4ml) and H2O. In the room temperature, it was added to the solution intense [inner (1ml) / said / naming] (400mg, 1.43mmol) and agitated over 3 hours through the syringe pump. This reaction mixture was agitated in the room temperature for 18 hours, and, subsequently carried out evaporation to dryness. Survival is pulverized and it is P2 O5. It dried under the high vacuum in the top, and the lithium salt of N-{{N-methyl-N-(2-pilus JINIRU methyl) amino} Carbonyl} valine was obtained (390mg, 100%). said lithium salt -- N-tert-butyl -1 -- according to coupling actuation of an example 8, coupling was carried out to the - {3(S)-amino-2(R)-hydroxy-4-phenyl butyl}-4(R)-(phenylthio) piperidine-2 (S)-carboxamide (manufactured by the hydrogenolysis of the compound 1 of Table II), and the mark compound of this example was obtained. A FAB mass spectrum and m/z:703(M+H)+.

[0051] Example 10 N-tert-butyl-1-{3 (-- S --) - {-- {(2, 6-dimethyl phenoxy) -- acetyl --} -- amino --} - two -- (-- R --) - hydroxy one - four - phenyl -- butyl --} - four -- (-- R --) - {(3-pilus JINIRU methyl) -- thio --} - - a piperidine - two -- (-- S --) - the carboxamide (formula 1;X= (2, 6-dimethyl phenoxy) acetyl --) B is R1 =H and R2 =C3 not existing (CH3). It reaches and Y is Boc by the manufacture usual approach of thio (3-pilus JINIRU methyl). By removing a protective group N-Boc to which the product indicated as a compound 14 of Table I of an example 5 corresponds A derivative It converted to the corresponding primary amine, i.e., the N-tert-butyl-1-(3 (S) - amino-2(R)-hydroxy-4-phenyl butyl)-4(R)-{(3-pilus JINIRU methyl) thio} piperidine-2-carboxamide. Primary amine was isolated as a gestalt of the tris hydrochloride. A compound (154mg, 0.27mmol), a latter acetic acid (2, 6-dimethyl phenoxy) (55.1mg, 0.31mmol), and latter BOP (147mg, 0.33mmol) were mixed in anhydrous [DMF] (4ml). DIEA (185microl, 1.06mmol) was added to this mixture. This mixture was agitated for 10 minutes in the room temperature. Furthermore the DIEA (95microl, 0 55mmol) part was added, and the obtained mixture was agitated in the same temperature for 18 hours. This reaction mixture is diluted by EtOAc (25ml), and they are the saturated water solution of NaHCO3, and H2O. And brine washed continuously, and concentration hardening by drying was dried and (MgSO4) carried out. ;(107mg, 64%) FAB mass spectrum and m/z:633(M+H)+ which refined survival with flash chromatography (inclination of eluate:0.1 %EtOH/EtOAc to SiO2 and 5%EtOH/EtOAc), and obtained the mark compound as a solid of light yellow.

[0052] example 11 recombination HIV protease assay: -- enzyme: -- {structure pBRT1prt+, W.G. Farr Mary et al., "Science", 236, and 305 (1987) reference}: which expressed the HIV protease in E.coli according to the following procedure -- all solutions are aquosity solutions unless it refuses especially.

(i) fermentation pBRT1prt+ Luria-BERUTA which uses the E.coli cell containing a plasmid and contains the ampicillin of 100microg / ml -- nib -- it ****(ed) to the inoculation culture medium which consists of a loss. It incubated in 37 degrees C, moving a flask violently for 17 hours. In the generation flask to which the ampicillin of 100microg / ml was supplied including sterilization M9 broth, it ****(ed) by 1% (v/v) of concentration using the above-mentioned inoculation culture. The full capacity in each generation flask was 500ml among the Erlenmeyer flask of 2L. Optical density 0.6 (lambda= 540nm) In 37 degrees C, it incubated, moving a flask violently until it became corresponding cell concentration (with no dilution). The range of this time amount is usually 3 - 4 hours. Subsequently, 5mM isopropyl thiogalactoside (IPTG, research auger NIKUSU, U.S. Ohio Cleveland) is supplied to a flask, and it sets to the dilution it is 16 times whose cell concentration of this, and is optical density 0.2. Incubation was continued until it became. subsequently, a flask -- 1mM phenylmethyl sulfonyl fluoride (PMSF) -- supplying -- base -- it refrigerated at 4 degrees C quickly. The centrifugal separation in 4 degrees C recovered this bacterial cell. The obtained humid pellet was saved in -70 degrees C.

[0053] (ii) The extract of the enzyme of an assay grade and especially all the processes of the manufacture following were performed in 4 degrees C, unless it refused. the frozen cell -- the buffer solution A -- {-- 50mM tris (hydroxymethyl) aminoethane HCl;(tris - HCl and pH7.4)0.6mM ethylenediaminetetraacetic acid (EDTA); -- to 0.375 MNaCl, 0.2 %NonidetP-40;(BDH (trademark) KEMIKARUZU Limited, British pool) 1mMPMSF}, and the cell weight 1 section, the buffer-solution A9 section came out comparatively, and it added. ** sow soil (cerite 545 (trademark), a JON man building, a ROM pock, U.S. California) was added at a rate of the two sections to the humid cell weight 1 section. The obtained slurry was homogenized at high

speed (about 20,000 rpm) on the wearing (trademark) industrial use blender by the pulse for 8x 15 seconds. It is the pellet which collected the fragment/cerite of a cell (trademark) according to centrifugal separation, and was obtained to the humid solid 1 section Buffer-solution A4.5 It extracted by the above-mentioned homogenization approach using the section. The supernatant liquid obtained from both the homogenization process was doubled, fusibility protein was settled by adding solid (NH4) 2SO4, and 75% saturation of the last concentration was obtained. This mixture was violently moved for 60 minutes, and centrifugal separation recovered precipitate. the obtained pellet -- buffer-solution B{50mM tris-HCl and pH8;30mMNaCl; 1mMDL-dithiothreitol (DTT); -- 1mMEDTA;1mMPMSF;10% glycerol} -- it suspended in inside and dialyzed to the same buffer solution for 18 hours.

[0054] It was filled up with the aliquot of the dialyzed extract containing 150mg of protein on the sephadex A25 (trademark) anion exchange column (Pharmacia, salary the Sweden country rise) which has the floor dimension of 70cm length, and the path of 2.5 cm. a sample -- a line -- in the 10cm [/hour] rate of flow, it eluted in isocratic one with the buffer solution B. The fraction (see the publication about the following assay) including HIV protease activity was doubled, the protein of fusibility was precipitated by adding saturated water nature (NH4) 2SO4, and 85% saturation of ** (NH4) 2SO4 concentration was obtained. They are buffer-solution C{50mM2-(4-morpholino) ethane sulfonic acid (MES) and pH5.5 about the pellet which removed precipitating protein according to centrifugal separation, and was obtained.;150mMNaCl;1mMDTT;1mMEDTA;10% glycerol} It dissolved in inside. This precipitate was dialyzed to the buffer solution C for 18 hours, and, subsequently it froze in -70 degrees C. By the same approach as the approach of the above-mentioned publication of all crude extracts, it was made the aliquot containing 150mg of protein, and the chromatography refined. The last manufactures obtained from each batch are collected, and it is 34microL. It divided into the aliquot and saved in -70 degrees C. The divided substrate / part / mg had the specific activity of the HIV protease of 18.2mmol(s), and the last protein collected from the fermentation of 20L was 300mg typically.

[0055] Before use, the aliquot was diluted to 1/38 of the first concentration with the buffer solution (refer to following) (namely, enzyme operation solution).

Substrate: VSFNFPQITL-NH2 and MW1164 (clough SURIHHI et al., "Proc.Natl.Acad.Sci.USA" 86,807 (1989) reference) were used as a substrate. This substrate was set to stock 10mM in DMSO, and was saved at 4 degrees C. Before use, this stock was diluted with the buffer solution and 400micro of solutions M was obtained (namely, substrate operation solution).

Buffer solution: It is the solution which dissolved MES (100mM), KCl (300mM), and EDTA (5mM) into distillation H2O (90ml), and was obtained by the dark aquosity NaOH 5.5 It adjusted. It is H2O about the latter solution. It diluted, and was referred to as 100ml, and the buffer solution was obtained.

[0056] Procedure: (1) assay mixture is substrate operation solution 20microl and solution 10microl of the trial compound in 10%DMSO. And enzyme operation solution 10microl It manufactured by mixing. (2) This assay mixture was incubated for 30 minutes in 37 degrees C. (3) About reagin, it is 2% aquosity trifluoroacetic acid 200microl. It quenched by adding. (4) Assay mixture 100microl which it quenched ****** given to HPLC which uses Perkin-Elmer 3x3CRC8 column (no [PerkinElmer, Incorporated and U.S. Connecticut] work piece) by the gradual inclination in a part for 4ml/of the rates of flow separated the substrate and the product (namely, VSFNF and PQITL-NH2). The following passes, it comes out and this inclination is certain :0.0-0.5. 70%A/part and 30%B;

0.5-3.0 67%A/Part and 33%B;

3.0-5.0 20%A/Part and 80%B;

5.0-6.5 70%A/Part and 30%B;

(Above A is H2O It is inner 3mM sodium dodecyl sulfate / 0.05%H3PO4, and B is 0.05%H3PO4 among an acetonitrile) . Elution was supervised in 210nm. (5) The contrast which is assay mixture without a trial compound was given to processes 2-4 at coincidence.

[0057] Consideration of inhibition: The quantum of a division product and the parent substrate of survival was carried out according to the integral of the height of a peak, or a suitable HPLC peak. The enzyme inhibition of the :inversion (%) =(peak height [of the sum total / substrate of the peak height of a product or a peak area, and a product] or sum total of peak area) x100 trial compound which computed substrate inversion using the following relational expression was computed as follows.

The concentration 50 of the trial compound which brings about 50% inhibition of an inhibition (%) =100-(inversion of inversion (%) / contrast of assay mixture (%)) x100HIV-protease, i.e., IC, measured the inhibition percentage of :enzyme measured as follows about the min of three different concentration of a trial compound. Then, it determined on the graph by plotting the inhibition percentage of an enzyme [as

opposed to the concentration of a trial compound for IC50]. IC50 of some instantiation compounds of a formula 1 measured in recombination HIV protease HPLC assay is hung up over Table IV after the following example.
[0058] Adaptation [the following procedure used in order to screen the anti-virus effectiveness of the compound of example 12 formula 1 / assay / using the cell which was already reported by above-mentioned Harada and others and by which the HTLV-I transformation was carried out / plaque]. Since the rate which HIV reproduces in a cell with it was quick, the cell by which the HTLV-I transformation was carried out was used. 1. Dissolve a trial compound into dimethyl sulfoxide and carry out concentration in 5mg/ml. The obtained solution can be stored at 4 degrees C to use.
2. Dilute the obtained solution in RPMI1640 (Gibco Laboratories, U.S. Massachusetts Lawrence), and make it into 4 times of the last concentration examined. If it dilutes in RPMI1640, this solution will be used within 4 hours in cell culture assay.
3. This 4X solution (50microl) was added to 3 section well of the flat bottom fine titration plate of 96 wells. RPMID (50microl) is added also to a contrast well.
4. RPMI1640(pH=7.2) 50microL by which the HEPES buffer was carried out inner C -- the fetal calf serum (FCS) and 12.5microl/ml gentamycin (perfect medium) by which the heat inactive compound was carried out 10% are added to all wells 8166 cells (5x104).
5. Perfect-medium 100microl The H9-/HTLV-IIIB stock (saved in liquid nitrogen as cell culture supernatant liquid in 50%FCS) of inner 50 time TCID50 is added to all wells. The infection titration value of a virus stock is the same as what was beforehand determined by the dilution terminal point on C8166 cell. The titration value of a stock is stable for 6 to 12 hours, when saved in -193 degrees C.
6. Subsequently, they are 37 degrees C and 5%CO2 about a fine titration plate. It puts on level shelving of the incubator made humid for 72 hours.
[0059] 7. Subsequently, remove a plate and measure the core of the syncytium in each well with a low power phase optical microscope. Each cluster of the cell which shows the proof of formation of some syncytiums is measured as one core of syncytium. A contrast well has the core of the syncytium of 25-75 for every well.
8. Compute the inhibition percentage of syncytial formation by the following formula.
Inhibition (%) =100x {(syncytium core in the syncytium core-# trial well in # contrast well) /(syncytium core in # contrast well)}
the concentration 50 of the trial compound which brings about 50% inhibition of syncytial formation, i.e., EC, plots on a graph the inhibition percentage by which the serial dilution technique of the operation solution of a process 3 was used, and the syncytial formation to the trial compound of various concentration was observed -- un--- a line -- it is determined using regression analysis. It was obtained from the recombination HIV protease HPLC assay of an example 10, and (namely, IC50 (nM)) the result of the assay of the instantiation compound of the formula (namely, EC50 (nM)) 1 obtained from the plaque assay of an example 11 is shown in the following table IV. Note that EC50 is not measured about some of compounds shown all over Table IV (ND).
[0060]
[Table 4]
Table IV Number Compound IC50 EC50 (nM) (nM)
---------- 1 N-tert-butyl-1-{3(S)-(benzyl- 9.5 ND oxy carbonyl amino)-2(R)- hydroxy-4-(4-fluoro phenyl)- butyl}-4(R)-(phenylthio)- Piperidine-2(S)-carboxamide (it indicates in the example 5)
2 N-tert-Butyl-1-{3(S)-(Benzyl- 400 ND Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenyl Piperidine -2 (S) - Carboxamide (Compound 1 of Table I)
3 N-tert-Butyl-1-{3(S)-(Benzyl- 460 ND Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Benzyl Piperidine -2 (S) - Carboxamide (Compound 2 of Table I)
4 N-Tert-Butyl-1-{3(S)-(Benzyl- 30 1400 Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenyl Sulfonyl - Piperidine-2(S)-Carboxamide (Compound 3 of Table I)
[0061]
5 N-tert-Butyl-1-{3(S)-(Benzyl- 10 800 Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenylthio - Piperidine-2(S)-Carboxamide (Compound 4 of Table I)
6 N-tert-Butyl-1-{3(S)-(Benzyl- 53 ND Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenoxy Piperidine -2 (S) - Carboxamide (Compound 5 of Table I)
7 N-tert-Butyl-1-{3(S)-(Benzyl- 2100 ND Oxy Carbonyl Amino)-2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Cyclohexyl Piperidine -2 (S) - Carboxamide (Compound 7 of Table I)

8 N-tert - Butyl - One - {-- Three -- (-- S --) - {-- {-- N - -- 3.9 -- -- 13 -- -- Benzyloxycarbonyl -- Valyl --} -- Amino --} - -- Two -- (-- R --) - Hydroxy One - Four - Phenyl -- Butyl --} - 4(R)-(Phenylthio) Piperidine - 2 (S)-Carboxamide (Compound 1 of Table II)
9 N-tert - Butyl - One - {-- Three -- (-- S --) - {-- {-- N - -- Four -- -- 43 -- (Benzyloxycarbonyl) - -- Asparaginyl --} -- Amino --} - Two -- (-- R --) - -- Hydroxy One - Four - Phenyl -- Butyl --} - 4(R)-(Phenylthio) Piperidine - 2(S)-Carboxamide (Compound 2 of Table II)
[0062]
10 N-tert - Butyl - One - {-- Three -- (-- S --) - {-- {-- N - -- 3.1 -- -- 90 -- (Benzyloxycarbonyl) - -- Valyl --} -- Amino --} - Two -- (-- R --) - -- Hydroxy One - Four - Phenyl -- Butyl --} - 4(R)-Phenyl Piperidine -2 (S) - Carboxamide (Compound 4 of Table II)
11 N-tert - Butyl - One - {-- Three -- (-- S --) - {-- {-- N - -- 3.7 -- -- 700 -- (Benzyloxycarbonyl) - -- Isoleucyl --} -- Amino --} - Two -- (-- R --) - -- Hydroxy One - Four - Phenyl -- Butyl --} - 4(R)-Phenyl Piperidine -2 (S) - Carboxamide (Compound 5 of Table II)
12 N-tert-Butyl-1-{3(S)-{N- 6.3 150 (Benzyloxycarbonyl)- Asparaginyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenyl Piperidine -2 (S) - Carboxamide (Compound 6 of Table II)
13 N-tert-Butyl-1-{3(S)-{N- 4.1 40 (Benzyloxycarbonyl)- Valyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenyl Piperidine -2 (S) - Carboxamide (Compound 7 of Table II)
14 N-tert-Butyl-1-{3(S)-{N- 2.3 40 (Benzyloxycarbonyl)- Valyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-(Phenyl Sulfonyl)- Piperidine-2(S)-Carboxamide (Compound 8 of Table II)
[0063]
15 N-Tert-Butyl-1-{3(S)-{N- 2.9 1270 (Benzyloxycarbonyl)- Asparaginyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-(Phenyl Sulfonyl)- Piperidine-2(S)-Carboxamide (Compound 9 of Table II)
16 N-Tert-Butyl-1-{3(S)-{N- 2.7 150 (Benzyloxycarbonyl)- Valyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenoxy Piperidine - 2(S)-Carboxamide (Compound 10 of Table II)
17 N-tert-Butyl-1-{3(S)-{N- 2.5 42 (Benzyloxycarbonyl)- Asparaginyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Phenoxy Piperidine - 2(S)-Carboxamide (Compound 11 of Table II)
[0064]
18 N-tert-Butyl-1-{3(S)-{N- 1.8 56 (Benzyloxycarbonyl)- Valyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-(2-Pilus JINIRU Oxy-)- Piperidine-2(S)-Carboxamide (Compound 12 of Table II)
19 N-Tert-Butyl-1-{3(S)-{N- 8 200 (Benzyloxycarbonyl)- Valyl} Amino} -2(R)- Hydroxy-4-Phenyl Butyl} - 4(R)-Cyclohexyl Piperidine - 2(S)-Carboxamide (Compound 13 of Table II)
20 N-tert-Butyl-1-{2 Phenyl [(R)- 3.1 12 Hydroxy-4-] -3 (S) - [ ] -- {(N- (2-KINORI Nil Carbonyl)) Valyl} amino} butyl}-4(R)- (phenylthio) Piperidine -2 (S) - Carboxamide (mark compound of an example 7)
21 N-tert-Butyl-1-{2(R)- 5.4 15 Hydroxy-4-Phenyl-3(S)- {{N-(2-KINORI Nil Carbonyl)- Asparaginyl} Amino} Butyl} - 4(R)-Phenoxy Piperidine -2 (S) - Carboxamide (Compound 1 of Table III)
22 N-tert-Butyl-1-{2(R)- 4.7 450 Hydroxy-4-Phenyl-3(S)- {{N-(2-KINORI Nil Carbonyl)- Asparaginyl} Amino} Butyl} - 4(R)-(Phenyl Sulfonyl) Piperidine - 2(S)-Carboxamide (Compound 2 of Table III)
[0065]
23 N-Tert-Butyl-1-{2(R)- 1.8 10 Hydroxy-4-Phenyl-3(S)- {{N-(2-KINORI Nil Carbonyl)- Asparaginyl} Amino} Butyl} - 4(R)-(Phenylthio) Piperidine - 2(S)-Carboxamide (Compound 3 of Table III)
24 N-tert-Butyl-1-{2(R)- 2.3 [16 Hydroxy-4-Phenyl-3(S)-] {{N-(2-North America Free Trade Agreement RENIRU Carbonyl)- Valyl} Amino} Butyl} -4(R)- (Phenylthio) Piperidine -2 (S) - Carboxamide (Compound 4 of Table III)
25 N-tert - Butyl - One - {-- Two -- (-- R --) - -- 1.9 -- -- 33 -- -- Hydroxy One - Three -- (-- S --) - {-- {-- N - (2- North America Free Trade Agreement RENIRU Carbonyl) - -- Asparaginyl --} -- Amino --} - Four - -- Phenyl -- Butyl --} -4 (R) - (Phenylthio) Piperidine -2 (S) - Carboxamide (Compound 5 of Table III)
26 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 3.5 -- -- 24 -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl - -} -- Amino --} - Two -- (-- R --) - -- Hydroxy One - Four - (4-Fluoro Phenyl) - -- Butyl --} - Four -- (-- R --) - (Phenylthio) - Piperidine-2(S)-Carboxamide (it Indicates in the Example 6)
[0066]
27 N-tert - Butyl - One - {-- Two -- (-- R --) - -- 4.9 -- -- 500 -- -- Hydroxy Ones - Four - Phenyl - Three -- (- - S --) - -- {-- {-- N - {(2-Pilus JINIRU-Methoxy) - -- Carbonyl --} -- Isoleucyl --} -- Amino --} - -- Butyl -- } - Four -- (-- R --) - Phenyl -- Piperidine - -2(S)-Carboxamide (Mark Compound of Example 8)
28 N-tert-Butyl-1-{3(S)- 16 500 (Benzyloxycarbonylamino)- 2(R)-Hydroxy-4-Phenyl- Butyl}-4(R)-(2-PIRIJI Nil Thio)- Piperidine-2(S)-Carboxamide (Compound 8 of Table I)

29 N-tert-Butyl-1-{3(S)- 8 140 (Benzyloxycarbonylamino)- 2(R)-Hydroxy-4-Phenyl- Butyl}-4(R)-(4-PIRIJI Nil Thio)- Piperidine-2(S)-Carboxamide (Compound 9 of Table I)
30 N-tert-Butyl -1 - {3(S)- 19 822 (Benzyloxycarbonylamino)- 2(R)-Hydroxy-4-Phenyl- Butyl}-4(R)-(2-Pyrimidinyl- Thio) Piperidine-2(S)-Carboxamide (Compound 10 of Table I)
[0067]
31 N-tert - Butyl-1-{3(S)- 12 290 (Benzyloxycarbonylamino)- 2(R)-Hydroxy-4-Phenyl- Butyl}-4(R)-(4, 6-Dimethyl- 2-Pyrimidinyl Thio) Piperidine - 2(S)-Carboxamide (Compound 11 of Table I)
32 N-tert-Butyl-1-{3(S)- 10 ND (Benzyloxycarbonylamino)- 2(R)-Hydroxy-4-Phenyl- Butyl}-4(R)-(Benzyl Thio)- Piperidine-2(S)-Carboxamide (Compound 12 of Table I)
33 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 3.2 -- -- 11 -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl - -} -- Amino --} - Two -- (-- R --) - Hydroxy One - -- Four - Phenyl -- Butyl --} -4 (R) - (2-PIRIJI Nil Thio) Piperidine - 2(S)-Carboxamide (Compound 14 of Table II)
34 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 2.5 -- -- 11 -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl - -} -- Amino --} - Two -- (-- R --) - Hydroxy One - -- Four - Phenyl -- Butyl --} -4 (R) - (4-PIRIJI Nil Thio) Piperidine - 2(S)-Carboxamide (Compound 15 of Table II)
[0068]
35 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 3.7 -- -- 15 -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl - -} -- Amino --} - Two -- (-- R --) - Hydroxy One - -- Four - Phenyl -- Butyl --} -4 (R) - (2-Pyrimidinyl Thio) Piperidine - 2(S)-Carboxamide (Compound 16 of Table II)
36 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 3.0 -- -- Nine -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl --} -- Amino --} - Two -- (-- R --) - Hydroxy One - -- Four - Phenyl -- Butyl --} -4 (R) - (4, 6-Dimethyl-2-Pyrimidinyl Thio) - Piperidine-2(S)-Carboxamide (Compound 17 of Table II)
37 N-tert - Butyl - One - {-- Three -- (-- S --) - -- 2.3 -- -- Seven -- -- {-- {-- N - (Benzyloxycarbonyl) - -- Valyl --} -- Amino --} - Two -- (-- R --) - Hydroxy One - -- Four - Phenyl -- Butyl --} -4 (R) - (Benzyl Thio) - Piperidine -2 (S) - Carboxamide (Compound 18 of Table II)
38 N-tert - Butyl - One - {-- Two -- (-- S --) - -- 4.3 -- -- 14 -- -- Hydroxy One - Three -- (-- S --) - {-- N - {-- {-- N - -- Methyl - N - (2-Pilus JINIRU Methyl) - -- Amino --} -- Carbonyl --} -- Valyl --} - Four - -- Phenyl -- Butyl --} - Four -- (-- R --) - Phenylthio) - Piperidine-2(S)-Carboxamide (Mark Compound of Example 9)
The compound of others of the formula 1 manufactured by the approach of a publication in a ---------- ---------- book specification is shown in Tables V, VI, and VII with EC50 (nM) as a result of being obtained from IC50 (nM) as a result of being obtained from the data of the property-ized mass spectrum, and the recombination HIV protease HPLC assay of an example 11, and the plaque assay of an example 12.
[0069]
[Table 5]
Table V number Formula N-tert-butyl-1-{2(R)- FAB/MS IC50 EC50 Hydroxy-4-phenyl -3 (S) - (m/z) (nM), (nM) {{N-(2-KINORI nil carbonyl)- (M+H) + Valyl} amino} butyl}-Y-piperidine - 2-carboxamide (Y is shown below among a formula) a passage -- it is -- compound of the formula 1 which it has ---------- ---------- 1 4 (R) -(2-pyrimidinyl thio) 712 3.6 7 2 4(R)-{(4-pilus JINIRU methyl)- 725 2.8 4 thio} 34 (R) -(2-pilus JINIRU methoxy) 709 3.9 244 4(R)-{(4 6 - dimethyl-2- 740 2.7 8 pyrimidinyl) thio}
5 4(R)- (4-PIRIJI Nil Thio) 711 1.5 3 6 4(R)- (2-PIRIJI nil thio) 711 1.9 4 7 4(R)-phenoxy 694 3.4 14 8 4 (R)-{(3-pilus JINIRU methyl)- 725 2.2 3 thio}
9 4(R)-{(2-Pilus JINIRU Methyl)- 725 4.2 5 Thio}
10 4(R)- (2-Pyrimidinyl Oxy-) 696 4(R)- {3.2 (4) 25 11 [6-dimethyl-2-] 724 4.0 20 pyrimidinyl oxy-} 4(R)-{12 () [4-methyl-2-] 710 4.5 44 Pyrimidinyl oxy-} 13 4(R)-{(2 6 - dimethyl-4- 724 3.6 17 pyrimidinyl) oxy-}
14 4(R)- (Phenyl Sulfonyl) 756 2.9 23 15 4(R)-{(4-Fluoro Phenyl)- 712 2.6 22 Oxy-}
16 4(R)- (4-Pilus JINIRU Methoxy) 709 4.2 22 17 4(R)-{(2-Pilus JINIRU Methyl)- 757 2.4 33 Sulfonyl}
18 4(R)-{(3-Pilus JINIRU Methyl)- 757 1.8 67 Sulfonyl}
19 4(R)-{(4-Pilus JINIRU Methyl)- 757 4.6 73 Sulfonyl}
20 4(R)- (2-Pilus JINIRU Sulfonyl) 743 1.7 13 21 4(R)- (4-Pilus JINIRU Sulfonyl) 743 1.7 25 22 4(R)-{(2 6 - Dimethyl-4- 740 2.4 11 Pyrimidinyl) Thio}
23 4(R)-{(4 - Methyl-2- 726 2.8 16 Pyrimidinyl) Thio 24 -- 4(R)-(3-Pilus JINIRU Methoxy) 709 3.7 53 ---------- ---------- ---------- [0070]
[Table 6]
front VI number formula N-tert-butyl -1 -{2(R)- FAB/MS IC50 EC50 -- hydroxy-4-phenyl-3(S)- (m/z) (nM) (nM)

{{N-(2-KINORI nil carbonyl)- (M+H) + B} amino} butyl}-Y-piperidine - 2-carboxamide (B and Y among a formula) the following -- being shown -- the compound of the formula 1 which it has -- ---------- ---------- B Y---------- -- 1 -tert-butyl - 4(R)- (phenyl- 724 3.0 12 glycyl thio)
2 Asparaginyl 4(R)-{(4 6- 755 2.2 42 Dimethyl-2-PIRIMI- JINIRU)} Thio 3 Asparaginyl 4 (R) - (2-PIRIMI 727 2.1 60 -JINIRUCHIO)
4 - (N4-MECHI- 4(R)-Phenoxy 723 3.7 13 RU) ASUPARAGI - Nil 5 -Tert-Butyl - 4(R)-{(3-Pilus- 740 2.2 8 Glycyl JINIRU Methyl) Thio}
6 Threo Nil 4 (R) - (Phenyl- 744 2.6 61 Sulfonyl)
7 -Tert-Butyl - 4 (R) - (4-PIRIJI- 757 2.1 29 Glycyl Nil Sulfonyl)
8 -Tert-Butyl - 4 (R) - (2-PIRIJI- 757 2.9 44 Glycyl Nil Sulfonyl)
---------- [0071]
[Table 7]
table VII number formula N-tert-butyl -1-{3{[(S)- FAB/MS IC50 EC50] {X} amino}-2(R)-hydroxy- (m /z) (nM) (nM)
4-phenyl butyl}-Y-piperidine - (M+H) + - 2(S)-carboxamide (it reaches X among a formula) Y -- the following -- being shown -- the compound of the formula 1 which it has -- ---------- X Y ---------- 1* (2, 6-G 4(R)-{(3- 633 2.7 35 methyl FENO- pilus JINIRU methyl)- KISHI-acetyl thio})
2 2, 4, 6- 4 (R) - (4- 633 3.7 47 Trimethyl FENO- PIRIJI Nil Thio)
KISHI acetyl 3 Phenoxy - 4 (R) - (4- 591 34 ND acetyl PIRIJI nil thio)
4 2, 6-G 4 (R) - (4- 619 3.1 20 Methyl FENO- PIRIJI Nil Thio)
KISHI-acetyl 5 (2-methyl- 4(R)-(4- 605 6.2 140 phenoxy)- PIRIJI nil thio)
Acetyl 6 (2, 4-G 4(R)-(4- 629 5.4 340 chlorophenyl)- PIRIJI nil thio)
Carbonyl 7 (2, 5-G 4(R)-(4- 629 9.8 360 chlorophenyl)- PIRIJI nil thio)
Carbonyl (2, 6-G 4(R)- (4- 597 14 340 fluoro- PIRIJI nil thio)) 8
Phenyl - (5-fluoro- 4(R)- (4- 593 6.8 ND 2-methyl- PIRIJI nil thio)) Carbonyl 9
Phenyl - Carbonyl ---------- [0072] * The manufacture approach of the compound number 1 is indicated by the example 10.
As an example of others of the compound of a formula 1 The following it can mention -- : -- N-tert - butyl - one - {-- two -- (-- S --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-KINORI nil carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - (4-PIRIJI nil thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N - tert - butyl - one - {-- four - (4-fluoro phenyl) - two -- (-- R --) - hydroxy one - three -- (-- S --) - {-- {-- N - (2-North America Free Trade Agreement RENIRU carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - (2-pyrimidinyl thio) -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-pilus JINIRU carbonyl) -- the valyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenoxy -- a piperidine - two -- (-- S --) - the carboxamide -- N-tert - butyl - one - {-- two -- (-- R --) - hydroxy one - four - phenyl - three -- (-- S --) - {-- {-- N - (2-pilus JINIRU carbonyl) -- the asparaginyl --} -- amino --} -- butyl --} - four -- (-- R --) - phenoxy -- a piperidine - two -- (-- S --) - the carboxamide .

[Translation done.]

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(30)Priority
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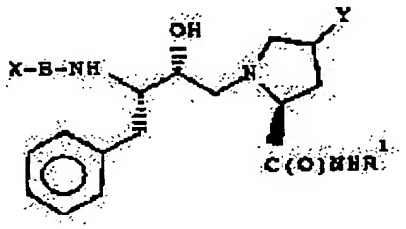
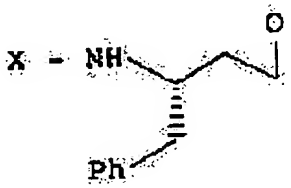
(54) SUBSTITUTED PYRROLIDINE DERIVATIVE AND HIV PROTEASE INHIBITOR

(57)Abstract:
PURPOSE: To obtain compounds having inhibiting activity of human immunodeficiency virus protease, which are useful in the treatment of HIV infections.
CONSTITUTION: Compounds of formula I [X is an R2OD(O), R2NR3C(O) or the like; R2 is a lower alkyl, phenyl or the like; R3 is H or a lower alkyl; R1 is a lower alkyl or lower cycloalkyl; Y is a lower alkyl, lower cycloalkyl, phenyl or the like; B is absent or a divalent group -NHCHR4C(O)-; R4 is a lower alkyl or the like], such as 4(S)-benzyloxy-1{3(S)-{[N-(benbyloxyloxycarbonyl)- valyl]amino}-2(R)-hydroxy-4-phenylbutyl}-N-tert-butylpyrrolidine-2(S)-carboxamide. The compd. of the formula I is obtained by reacting an epoxide of the formula II with pyrrolidinecarboxamide of formula III.



I



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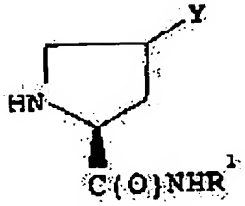

III

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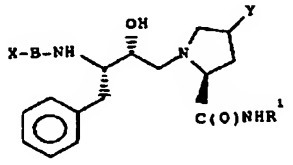
最終頁に続く

(54)【発明の名称】　置換ピロリジン誘導体及びＨＩＶプロテアーゼ阻害剤

(57)【要約】
【構成】　式１
【化１】



１

（式中、Ｘは末端基、例えばアリールオキシカルボニルまたはアルカノイルであり；Ｂは存在しないか、またはアミノ酸残基、例えばVal またはAsn であり；R^1 はアルキルであり；及びＹは環置換基、例えばベンジル、ベンジルオキシ、フェニルチオまたは２－ピリジニルチオである）で示される化合物が開示されている。
【効果】　本化合物は、ヒト免疫不全ウィルス（ＨＩＶ）プロテアーゼの活性を阻害し、ヒト細胞中のＨＩＶ誘導された細胞病原性効果を抑制する。このような特性を有しているので、本化合物はＨＩＶ感染症の撃退のために有効である。

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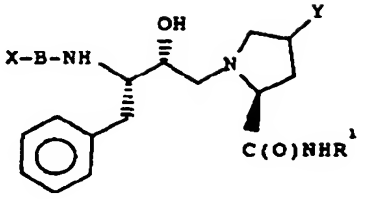
【特許請求の範囲】

【請求項１】　式１

【化１】



１

で示される化合物または治療学的に許容され得るその酸付加塩。〔ただし、式中、Xは、R^2 OC（O）、R^2 C（O）またはR^2 NR^3 C（O）であり（式中、R^2は、

（i）低級アルキル、

（ii）低級シクロアルキル、

（iii)フェニルまたはハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより１置換されたフェニル、

（iv）フェニル（低級）アルキルまたはその芳香族部分がハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより１置換されたフェニル（低級）アルキル、

（v）１－ナフチルまたは２－ナフチル、

（vi）（Het)または（Het)－（低級アルキル）（Hetは、窒素、酸素またはイオウから選択された１または２のヘテロ原子を含む５または６員の１価の複素環基を示す）または

（vii)２－キノリニルまたは３－キノリニルであり、及びR^3は、水素または低級アルキルである）；またはXは、$R^{2A}OCH_2$ C（O）であり（式中、R^{2A}は、フェニルまたは低級アルキルもしくはハロゲンにより１置換、２置換または３置換されたフェニルである）；Bは、存在しないか、または２価の基－NHCHR^4 C（O）－であり（式中、R^4は低級アルキル；低級シクロアルキル；（低級シクロアルキル）－（低級アルキル）；フェニルメチル；またはヒドロキシ、カルボキシ、低級アルコキシカルボニル、アミノカルボニル、（低級アルキル）アミノカルボニルもしくはジ（低級アルキル）アミノカルボニルにより１置換された低級アルキルである）；R^1は、低級アルキルまたは低級シクロアルキルであり；Yは、低級アルキル；低級シクロアルキル；フェニルまたはハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより１置換されたフェニル；フェニルメチルまたはハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより１置換されたフェニルメチルであり；またはYは、$W(CH_2)_n$ Zである（式中、Wは、オキソ、チオ、スルフィニルまたはスルホニルであり、Zは、低級アルキル；フェニルまたは

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はハロゲン、ヒドロキシ、低級アルキル若しくは低級アルコキシにより１置換されたフェニル；または（Het)であり（式中、（Het)は、上記定義の通りである）；nは、０または１である。〕。

【請求項２】　式中、Xは、R^2 OC（O）またはR^2 C（O）であり（式中、R^2は、低級アルキル；フェニル（低級）アルキル；フェニル（低級）アルキル（フェニル部分の４位がクロロ、フルオロ、ヒドロキシ、メチルまたはメトキシにより置換されている）；１－ナフチル；２－ナフチル；２－フリル；２－チエニル；２－ピリジニル；４－ピリジニル；２－ピリジニルメチル；４－チアゾリルメチルまたは２－キノリニルである）；またはXは、$R^{2A}OCH_2$ C（O）であり（式中、R^{2A}は、フェニルまたは２、４及び６位からなる群から選択される１の位置または複数の位置において低級アルキルまたはハロゲンにより１、２または３置換されたフェニルである）；Bは、存在しないかまたは２価の基－NHCHR^4 C（O）－であり（式中、R^4は、低級アルキルまたはヒドロキシ、低級アルコキシカルボニル、アミノカルボニル、（低級アルキル）アミノカルボニルもしくはジ（低級アルキル）アミノカルボニルにより１置換された低級アルキルである）；R^1は、１－メチルエチル、１、１－ジメチルエチル、２－メチルプロピル、シクロブロピル、シクロブチル、シクロペンチルまたはシクロヘキシルであり；Yは、低級シクロアルキル、フェニル、４－クロロフェニル、４－ブロモフェニル、４－フルオロフェニル、４－メチルフェニル、４－メトキシフェニル、フェニルメチル、（４－フルオロフェニル）メチルまたは（４－メチルフェニル）メチルであり；または　Yは、$W(CH_2)_n$ Zであり（式中、W及びnは上記定義の通りであり、Zは低級アルキル、フェニル、２－フリル、２－チエニル、２－ピリジニル、３－ピリジニル、４－ピリジニル、４－チアゾリル、２－ピリミジニル、４、６－ジメチル－２－ピリミジニルまたは２、６－ジメチル－４－ピリミジニルである請求項１に記載の化合物または治療学的に許容され得るその酸付加塩。

【請求項３】　式中、Xは、tert－ブチルオキシカルボニル、ベンジルオキシカルボニル、（４－クロロ－フェニル）メトキシカルボニル、（４－ヒドロキシフェニル）メトキシカルボニル、（４－メトキシフェニル）メトキシカルボニル、アセチル、ベンゾイル、１－ナフタレニルカルボニル、２－ナフタレニルカルボニル、２－ピリジニルメトキシカルボニルまたは２－キノリニルカルボニル、フェノキシアセチル、（２－メチルフェノキシ）アセチル、（２、４－ジメチルフェノキシ）アセチル、（２、６－ジメチルフェノキシ）－アセチル、（２、４、６－トリメチルフェノキシ）アセチル、（４－クロロフェノキシ）アセチルまたは（４－フルオロ－２、６－ジメチルフェノキシ）アセチルであり；Bは、

存在しないか、または2価の基－NHCHR^{4}C（O）－であり（式中、R^{4}は、1－メチルエチル、1、1－ジメチルエチル、1－メチルプロピル、2－メチルプロピル、メトキシカルボニルメチル、エトキシカルボニル－メチルまたはアミノカルボニルメチルである）；R^{5}は、1、1－ジメチルエチルまたはシクロプロピルであり；Yは、シクロヘキシル、フェニル、4－クロロフェニル、4－フルオロフェニル、4－メトキシフェニル、ベンジル、（4－メトキシフェニル）メチル、2－メチルプロポキシ、フェノキシ、2－ピリジニルオキシ、3－ピリジニルオキシ、4－ピリジニルオキシ、2－ピリミジニルオキシ、4、6－ジメチル－2－ピリミジルオキシ、2、6－ジメチル－4－ピリミジニルオキシ、ベンジルオキシ、2－ピリジニルメトキシ、4－チアゾリルメトキシ、2－ピリミジニルメトキシ、フェニルチオ、フェニルスルフィニル、フェニルスルホニル、2－ピリジニルチオ、3－ピリジニルチオ、4－ピリジニルチオ、2－ピリミジニルチオ、4、6－ジメチルチオ－2－ピリミジニルチオ、ベンジルチオ、ベンジルスルフィニル、ベンジルスルホニル、（2－ピリジニルメチル）チオ、（3－ピリジニルメチル）チオまたは（4－ピリジニルメチル）チオである請求項2に記載の化合物または治療学的に許容され得るその酸付加塩。

【請求項4】　式中、Xは、tert－ブチルオキシカルボニル、ベンジルオキシカルボニル、アセチル、2－ナフタレニルカルボニル、2－ピリジニルメトキシカルボニル、2－キノリニルカルボニルであり；　Bは、バリル、イソロイシルまたはアスパラギニルであり；R^{1}は1、1－ジメチルエチル又はシクロプロピルであり；Yは、フェニル、ベンジル、フェノキシ、2－ピリミジニルオキシ、2、6－ジメチル－4－ピリミジニルオキシ、ベンジルオキシ、フェニルチオ、フェニルスルホニル、2－ピリジニルチオ、3－ピリジニルチオ、4－ピリジニルチオ、2－ピリミジニルチオ、4、6－ジメチル－2－ピリミジニルチオまたは（3－ピリジニルメチル）チオである請求項3に記載の化合物または治療学的に許容され得るその酸付加塩。

【請求項5】　式中、Xは、（2－メチルフェノキシ）アセチル、（2、4－ジメチルフェノキシ）－アセチル、（2、6－ジメチルフェノキシ）アセチルまたは（2、4、6－ジメチルフェノキシ）アセチルであり；Bは存在せず；R^{1}は1、1－ジメチルエチルであり；Yは、フェニル、ベンジル、フェノキシ、2－ピリミジニルオキシ、2、6－ジメチル－4－ピリミジニルオキシ、ベンジルオキシ、フェニルチオ、フェニルスルホニル、2－ピリジニルチオ、3－ピリジニルチオ、4－ピリジニルチオ、2－ピリミジニルチオ、4、6－ジメチル－2－ピリミジニルチオまたは（3－ピリジニルメチル）チオである請求項1に記載の化合物または治療学的に許容され得るその酸付加塩。

【請求項6】　4（S）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

4（S）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－4（S）－2－メチルプロピルオキシ）ピロリジン－2（S）－カルボキサミド、

1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－4（R）－（2－メチルプロピルオキシ）ピロリジン－2（S）－カルボキサミド、

4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－シクロプロピルピロリジン－2（S）－カルボキサミド、

4（R）－ベンジル－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

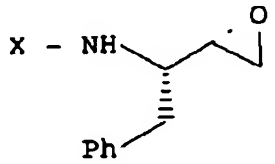
4（S）－ベンジル－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド、

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（2－ピリミジニルチオ）ピロリジン－2（S）－カルボキサミド、

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－｛（3－ピリジニルメチル）チオ｝ピロリジン－2（S）－カル

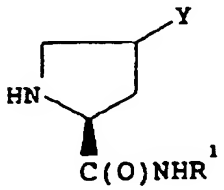
5

ボキサミド、
Ｎ－tert－ブチル－１－｛２（Ｒ）－ヒドロキシ－４－フェニル－３（Ｓ）－｛｛Ｎ－（２－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－４（Ｒ）－｛（２、６－ジメチル－４－ピリミジニル）オキソ｝ピロリジン－２（Ｓ）－カルボキサミド、
Ｎ－tert－ブチル－１－｛３（Ｓ）－｛｛（２、６－ジメチルフェノキシ）－アセチル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－２－ピリミジニルチオ）－ピロリジン－２（Ｓ）－カルボキサミド及び
Ｎ－tert－ブチル－１－｛３（Ｓ）－｛｛２、６－ジメチルフェノキシ）アセチル｝－アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－｛（３－ピリジニルメチル）チオ｝ピロリジン－２（Ｓ）－カルボキサミドからなる群から選択される請求項１に記載の化合物。
【請求項７】　請求項１に記載の化合物または治療学的に許容され得るその塩及び薬学的に許容され得る担体を含む薬学的組成物。
【請求項８】　有効量の請求項１に記載の化合物または治療学的に許容され得るその塩をヒトに投与することを含む、ヒトのＨＩＶ感染症を治療する方法。
【請求項９】　抗ＨＩＶ有効量の請求項１に記載の化合物または治療学的に許容され得るその塩によってヒトの細胞を処理することを含むヒトの細胞をＨＩＶ病原体から保護する方法。
【請求項１０】　下記工程：
（ａ）式２
【化２】



2

（式中、Ｘは、請求項１において定義した通りである）のエポキシドと、式３
【化３】

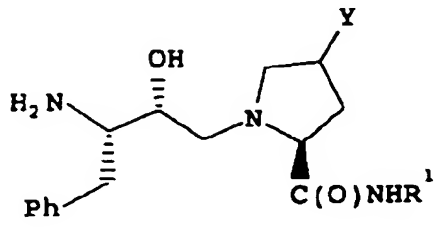


3

（式中、Ｒ¹ 及びＹは、請求項１において定義した通りである）のピロリジンカルボキサミドとを反応させて、

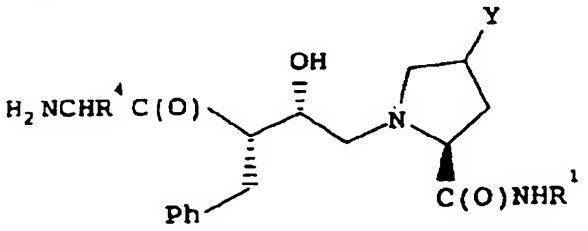
6

式１（式中、Ｘ、Ｒ¹ 及びＹは、上記定義の通りであり、Ｂは存在しない）の対応する化合物を得るか；または
（ｂ）式４
【化４】



4

（式中、Ｒ¹ 及びＹは、上記定義の通りである）の化合物と、カルボン酸Ｘ－ＯＨ（式中、Ｘは、請求項１において定義されたＲ² Ｃ（Ｏ）またはＲ²ＡＯＣＨ₂Ｃ（Ｏ）である）の反応性誘導体とを反応させて、式１（式中、Ｘは上記定義のＲ² Ｃ（Ｏ）またはＲ²ＡＯＣＨ₂Ｃ（Ｏ）であり、Ｒ¹ 及びＹは上記定義の通りであり、Ｂは存在しない）の対応する化合物を得るか；または
（ｃ）式４（式中、Ｒ¹ 及びＹは、上記定義の通りである）の化合物と、式Ｘ－ＮＨＣＨＲ⁴ ＣＯＯＨ（式中、Ｘ及びＲ⁴ は、請求項１の定義の通りである）のα－アミノ酸とを、カップリング剤の存在下でカップリングして、式１（式中、Ｘ、Ｒ¹ 及びＹは、上記定義の通りであり、Ｂは、２価の基－ＮＨＣＨＲ⁴ Ｃ（Ｏ）－である（式中、Ｒ⁴ は上記定義の通りである））の対応する化合物を得るか；または
（ｄ）式５
【化５】



5

（式中、Ｒ¹ 、Ｒ⁴ 及びＹは、上記定義の通りである）の化合物と、カルボン酸Ｘ－ＯＨ（式中、Ｘは、上記定義のＲ² Ｃ（Ｏ）またはＲ²ＡＯＣＨ₂Ｃ（Ｏ）である）の反応性誘導体とを反応させて、式１（Ｘは、上記定義のＲ² Ｃ（Ｏ）またはＲ²ＡＯＣＨ₂Ｃ（Ｏ）であり、Ｒ¹ 及びＹは、上記定義の通りであり、Ｂは２価の基－ＮＨＣＨＲ⁴ Ｃ（Ｏ）－である（式中、Ｒ⁴ は上記定義の通りである））の対応する化合物を得て；次いで、
（ｅ）所望により、上記セクション（ａ）、（ｂ）、（ｃ）または（ｄ）において得られた式１の化合物を、

対応する治療学的に許容され得る酸付加塩に変換することを含む請求項1に記載の式1の化合物または治療学的に許容され得る酸付加塩を製造する方法。

【発明の詳細な説明】

【0001】

【産業上の利用分野】本発明は、特定のレトロウィルスに対する活性を示す化合物、その化合物の製造方法、その薬学的処方物及びレトロウィルスにより生じる感染症を撃退するその化合物の使用方法に関する。

【0002】

【従来の技術】1983年に、ヒト免疫不全ウィルスタイプ1（HIV－1）として知られるレトロウィルスは、後天性免疫不全症候群（エイズ）の病原体として確立された。R．C．ガロ及びL．モンタニエールによる「Scientific American」、259（4）、40（1988）参照。このウィルスは、恐怖心を抱かせるほどの疫病となっている。より最近では、非常に関連するウィルス、ヒト免疫不全ウィルスタイプ2（HIV－2）が、エイズの第2の病原体として同定されている。病原体としてのヒト免疫不全ウィルス（HIV）を同定し、このウィルスを大量に成長させる方法を開発することによって、生体外でのHIVの複製を阻害する化合物が発見されている。この方法により同定された阻害化合物の最も重要な種類は、ジデオキシヌクレオシドの群であり、その3’－アジド－3’－デオキシチミジン（ジドブジンまたはAZTとしても知られている）及びより最近では、2’3’－ジデオキシイノシン（ジダノシンまたはDDIとしても知られている）が治療学的に使用されて、特定の患者を症候的なHIV感染症により管理している。この種の化合物は、逆転写を阻害することによりHIVのライフサイクルを妨げることが発見されている。この酵素は、ウィルスRNAを二本鎖デオキシリボ核酸（DNA）に転化し、それ自体HIV複製にとって必須の酵素である。逆転写の阻害の他に、HIVライフサイクルのその他の期が、抗HIV薬の開発のための標的として同定されている。高まる注意を受けている1の標的は、HIVプロテアーゼとして知られるHIVコードされた酵素である。この酵素は、逆転写酵素と同様に、pol遺伝子によりコードされ、HIVの成長に必須である。これは、gag（p55）またはgag－pol（p180）タンパク質中の特定の分割を行い、成熟感染性ビリオン中に見られる構造タンパク質（例えば、p17及びp24）及びそれ自体を含む酵素を放出する原因物質である。従って、HIVプロテアーゼの阻害剤は、HIVライフサイクルをブロックすることができる。

【0003】ここ数年にわたって、HIVプロテアーゼへ注がれた関心の増加は、酵素を阻害する物質の発見に関する報告の増加に反映している。例えば、D．W．ノーベック及びD．J．ケンブ、「Annual Reports In Medicinal Chemistry」、26、141（1991）によ

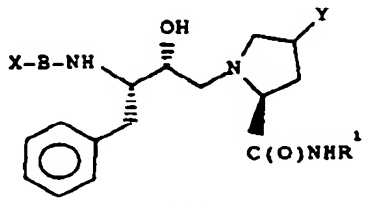
るプロテアーゼ阻害剤に関する細菌の論文参照。後者の論文において記載され、及びD．H．リッチら、「J．Med Chem．」、33、1285（1990）及びN．A．ロバーツら、「Science」、248、358（1990）により報告されているように、2つの強力なHIVプロテアーゼインヒビター系が、p17／p24基質分解部位配列を有するペプチド中に、ヒドロキシエチルアミン遷移状態類似物（TSA）を配置することによって理解されている。ロバーツらの連続の鉛化合物の生物学的研究は、H．A．オーバートンら、「Virology」、179、508（1990）、J．A．マーチンら、「Biochem.Biophys.Res.Commun．」176、180（1991）及びJ．C．クレイグら、「Antiviral Chemistry and Chemotheraphy」、2、181（1991）により報告されている。ヒドロキシエチルアミンTSAを有するHIVプロテアーゼ阻害剤のその他の開示は、下記のものを包含する：B．K．ハンダら、1989年12月20日に発行された欧州特許出願第346847号、G．B．ドレイヤーら、1990年1月24日に発行された欧州特許出願第352000号、D．J．ケンブら、1990年12月19日に発行された欧州特許出願第402646号、K．E．B．バーカーズら、1991年6月12日に発行されたカナダ国特許出願第2，030，415号、J．A．マーチン及びS．レッドショー、1991年6月19日に発行された欧州特許出願第432695号。

【0004】

【発明の構成】本出願は、その構造中に導入されたエチルアミンTSAを有する置換ピロリジン誘導体を開示する。これらの誘導体は、HIVプロテアーゼの強力な阻害剤である。さらに、ヒトの細胞中でHIV誘導された細胞病原性効果を阻害する能力が、これらの化合物について示されている。これらの特性並びに比較的選択的な作用及び明らかに毒性がないという特性を有しているので、その化合物はHIV感染症を撃退するための薬剤として有効である。本発明の化合物は、式1

【0005】

【化6】



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【0006】で示されるか、または治療学的に許容され得るその酸付加塩である。ただし、式中、Xは、$R^2OC(O)$、$R^2C(O)$または$R^2NR^3C(O)$であり（式中、R^2は、(i)低級アルキル、(ii)低級シクロアルキル、(iii)フェニルまたはハロゲン、ヒドロキ

シ、低級アルキルもしくは低級アルコキシにより1置換されたフェニル、(iv)フェニル(低級)アルキルまたは芳香族部分がハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより1置換されたフェニル(低級)アルキル、(v)1－ナフチルまたは2－ナフチル、(vi)(Het)または(Het)－(低級アルキル)(Hetは、窒素、酸素及びイオウから選択される1または2のヘテロ原子を含む5または6員の1価の複素環基を示す)、または(vii)2－キノリニルまたは3－キノリニルであり、及びR³は、水素または低級アルキルである)；またはXは、R²ᴬOCH₂C(O)であり(式中、R²ᴬは、フェニルまたは低級アルキルもしくはハロゲンにより1置換、2置換または3置換されたフェニルである)；

【0007】Bは、存在しないか、または2価の基－NHCHR⁴C(O)－であり(式中、R⁴は低級アルキル；低級シクロアルキル；(低級シクロアルキル)－(低級アルキル)；フェニルメチル；またはヒドロキシ、カルボキシ、低級アルコキシカルボニル、アミノカルボニル、(低級アルキル)アミノカルボニルもしくはジ(低級アルキル)アミノカルボニルにより1置換された低級アルキルである)；R¹は、低級アルキルまたは低級シクロアルキルであり；Yは、低級アルキル；低級シクロアルキル；フェニルまたはハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより1置換されたフェニル；フェニルメチルまたはハロゲン、ヒドロキシ、低級アルキルもしくは低級アルコキシにより1置換されたフェニルメチルであり；またはYは、W(CH₂)ₙZである(式中、Wは、オキソ、チオ、スルフィニルまたはスルホニルであり、Zは、低級アルキル；フェニルまたはハロゲン、ヒドロキシ、低級アルキル若しくは低級アルコキシにより1置換されたフェニル；または(Het)(式中、(Het)は、上記定義の通りである)であり；nは、0または1である)。

【0008】式1に関して本明細書中で使用される句「Bは存在しない」は、記号Bが「X」を、第2アミノ基(その他の場合には「B」と結合する)と結合させる共有結合となることを意味すると理解されたい。本発明の化合物の好適な群は、式1(式中、Xは、R²OC(O)またはR²C(O)であり(式中、R²は、低級アルキル；フェニル(低級)アルキル；フェニル(低級)アルキル(フェニル部分の4位がクロロ、フルオロ、ヒドロキシ、メチルまたはメトキシにより置換されている)；1－ナフチル；2－ナフチル；2－フリル；2－チエニル；2－ピリジニル；4－ピリジニル；2－ピリジニルメチル；4－チアゾリルメチルまたは2－キノリニルである)；またはXは、R²ᴬOCH₂C(O)であり(式中、R²ᴬは、フェニルまたは2、4及び6位からなる群から選択される1の位置または複数の位置において低級アルキルまたはハロゲンにより1、2または3置換されたフェニルである)；Bは、存在しないかまたは2価の基－NHCHR⁴C(O)－であり(式中、R⁴は、低級アルキルまたはヒドロキシ、低級アルコキシカルボニル、アミノカルボニル、(低級アルキル)アミノカルボニルまたはジ(低級アルキル)アミノカルボニルにより1置換された低級アルキルである)；R¹は、1－メチルエチル、1、1－ジメチルエチル、2－メチルプロピル、シクロプロピル、シクロブチル、シクロペンチルまたはシクロヘキシルであり；

【0009】Yは、低級シクロアルキル、フェニル、4－クロロフェニル、4－ブロモフェニル、4－フルオロフェニル、4－メチルフェニル、4－メトキシフェニル、フェニルメチル、(4－フルオロフェニル)メチルまたは(4－メチルフェニル)メチルであり；またはYは、W(CH₂)ₙZである(式中、W及びnは上記定義の通りであり、Zは低級アルキル、フェニル、2－フリル、2－チエニル、2－ピリジニル、3－ピリジニル、4－ピリジニル、4－チアゾリル、2－ピリミジニル、4、6－ジメチル－2－ピリミジニルまたは2、6－ジメチル－4－ピリミジニルである))で示されるかまたは治療学的に許容され得るその酸付加塩である。本発明の化合物のより好ましい群は、式1(式中、Xは、tert－ブチルオキシカルボニル、ベンジルオキシカルボニル、(4－クロロ－フェニル)メトキシカルボニル、(4－ヒドロキシフェニル)メトキシカルボニル、(4－メトキシフェニル)メトキシカルボニル、アセチル、ベンゾイル、1－ナフタレニルカルボニル、2－ナフタレニルカルボニル、2－ピリジニルメトキシカルボニル、2－キノリニルカルボニル、フェノキシアセチル、(2－メチルフェノキシ)アセチル、(2、4－ジメチルフェノキシ)アセチル、(2、6－ジメチルフェノキシ)－アセチル、(2、4、6－トリメチルフェノキシ)アセチル、(4－クロロフェノキシ)アセチルまたは(4－フルオロ－2、6－ジメチルフェノキシ)アセチルであり；

【0010】Bは、存在しないか、または2価の基－NHCHR⁴C(O)－であり(式中、R⁴は、1－メチルエチル、1、1－ジメチルエチル、1－メチルプロピル、2－メチルプロピル、メトキシカルボニルメチル、エトキシカルボニルメチルまたはアミノカルボニルメチルであり；R¹は、1、1－ジメチルエチルまたはシクロプロピルであり；Yは、シクロヘキシル、フェニル、4－クロロフェニル、4－フルオロフェニル、4－メトキシフェニル、ベンジル、(4－メトキシフェニル)メチル、2－メチルプロポキシ、フェノキシ、2－ピリジニルオキシ、3－ピリジニルオキシ、4－ピリジニルオキシ、2－ピリミジニルオキシ、4、6－ジメチル－2－ピリミジニルオキシ、2、6－ジメチル－4－ピリミジニルオキシ、ベンジルオキシ、2－ピリジニルメトキシ、4－チアゾリルメトキシ、2－ピリミジニルメトキシ

シ、フェニルチオ、フェニルスルフィニル、フェニルスルホニル、２－ピリジニルチオ、３－ピリジニルチオ、４－ピリジニルチオ、２－ピリミジニルチオ、４、６－ジメチル－２－ピリミジニルチオ、ベンジルチオ、ベンジルスルフィニル、ベンジルスルホニル、（２－ピリジニルメチル）チオ、（３－ピリジニルメチル）チオまたは（４－ピリジニルメチル）チオである）で示されるかまたは治療学的に許容され得るその酸付加塩である。

【００１１】本発明の化合物の最も好ましい群は、式１（式中、Ｘは、tert－ブチルオキシカルボニル、ベンジルオキシカルボニル、アセチル、２－ナフタレニルカルボニル、２－ピリジニルメトキシカルボニルまたは２－キノリニルカルボニルであり；Ｂは、バリル、イソロイシルまたはアスパラギニルであり；R^1 は、１、１－ジメチルエチルまたはシクロプロピルであり；及びＹは、フェニル、ベンジル、フェノキシ、２－ピリミジニルオキシ、２、６－ジメチル－４－ピリミジニルオキシ、ベンジルオキシ、フェニルチオ、フェニルスルホニル、２－ピリジニルチオ、３－ピリジニルチオ、４－ピリジニルチオ、２－ピリミジニルチオ、４、６－ジメチル－２－ピリミジニルチオまたは（３－ピリジニルメチル）チオである）で示されるか、または治療学的に許容され得るその酸付加塩である。本発明の化合物のその他の最も好ましい群は、式１（式中、Ｘは、（２－メチルフェノキシ）アセチル、（２、４－ジメチルフェノキシ）アセチル、（２、６－ジメチルフェノキシ）アセチルまたは（２、４、６－ジメチル－フェノキシ）アセチルであり；Ｂは存在せず；R^1 は１、１－ジメチルエチルであり；及びＹは直前に定義した通りである）で示されるかまたは治療学的に許容され得るその酸付加塩である。式１（式中、Ｂは２価の基－ＮＨＣＨＲ^4 Ｃ（Ｏ）－である）の化合物に関して、R^4 を担持する不斉炭素原子は、（Ｓ）配置を有することが好ましい。

【００１２】本発明の範囲内には、式１の化合物または治療学的に許容され得るその塩と薬学的に許容され得る担体とを含む、ヒトのＨＩＶ感染症の治療のための薬学的組成物が含まれる。本発明の範囲は、有効量の式１の化合物または治療学的に許容され得るその塩とをヒトに投与することを含む、ヒトのＨＩＶ感染症を治療する方法をも包含する。その範囲にはまた、ヒトの細胞を、抗ＨＩＶ有効量の式１の化合物または治療学的に許容され得るその塩により処理することを含む、ヒトの細胞をＨＩＶ病原体から保護する方法が包含される。式１の化合物の製造方法を以下に説明する。一般的に、アミノ酸及び保護基を表示するために本明細書中で使用される略語は、生化学命名ＩＵＰＡＣ－ＩＵＢ委員会の勧告に準拠したものである。「European Journal of Biochemistry」１３８、９（１９８４）参照。例えば、Val 、Ile 、Asn 及びLeu は、それぞれＬ－バリン、Ｌ－イソロイシン、Ｌ－アスパラギン及びＬ－ロイシンの残基を示す。単独または１の基と組合せて本明細書において用いられる語句「低級アルキル」は、１～６の炭素原子を含む直鎖状のアルキル基及び３～４の炭素原子を含む分枝鎖状のアルキル基を意味し、メチル、エチル、プロピル、ブチル、ヘキシル、１－メチルエチル、１－メチルプロピル、２－メチルプロピル及び１、１－ジメチルエチルを包含する。

【００１３】単独または１の基と組合せて本明細書において用いられる語句「低級シクロアルキル」は、３～６の炭素原子を含む飽和環式炭化水素基を意味し、シクロプロピル、シクロブチル、シクロペンチル及びシクロヘキシルを包含する。本明細書において用いられる語句「低級アルコキシ」は、１～６の炭素原子を含む直鎖状のアルコキシ基及び３～４の炭素原子を含む分枝鎖状のアルコキシ基を意味し、メトキシ、エトキシ、プロポキシ、ヘキソキシ、１－メチルエトキシ、ブトキシ及び１、１－ジメチルエトキシを包含する。後者の基は、tert- ブチルオキシとして通常知られている。本明細書中において用いられる語句「ハロゲン」は、臭素、塩素、フッ素、ヨー素から選択されるハロゲン基である。本明細書中において用いられる語句「Het 」は、窒素、酸素及びイオウから選択される１～２のヘテロ原子を含む５または６員の飽和または不飽和複素環から水素が除去されて得られる１価の基である。任意に、この複素環は、１または２の置換基；例えば、低級アルキル、低級アルコキシ、ハロゲン、アミノまたは低級アルキルアミノを有していてもよい。適当な複素環及び任意に置換された複素環の例は、ピロリジン、テトラヒドロフラン、チアゾリジン、ピロール、１Ｈ－イミダゾール、１－メチル－１Ｈ－イミダゾール、イソキサゾール、チアゾール、２－メチルチアゾール、２－アミノチアゾール、ピペリジン、１、４－ジオキサン、４－モルホリン、ピリジン、２－メチルピリジン、ピリミジン、４－メチルピリミジン及び２、４－ジメチルピリミジンを包含する。アミノ酸に関する語句「残基」は、カルボキシ基のヒドロキシルまたはα－アミノ基の１の水素を除去することによって、対応するα－アミノ酸から得られる基を意味する。

【００１４】本明細書中において用いられる語句「薬学的に許容され得る担体」は、活性成分に有害な作用を与えず、活性成分のための無毒で一般的に不活性の賦形剤を意味する。本明細書中において用いられる語句「有効量」は、生体内においてＨＩＶに対して十分に有効である本発明の化合物の予め定められた量を意味する。一般的に、式１の化合物は、反応体にとって適していることが知られている反応条件を使用して、知られた方法により製造される。方法の記載は、「Annual Reports In Organic Synthesis －1990」Ｋ．ターンバルらによる編集、アカデミックプレスインコーポレイテッド、米国カリフォルニア州サンディエゴ、１９９０（及び上記の

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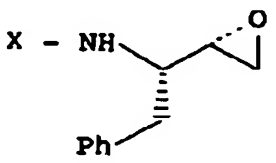
「annual reports」）、「Vogel's Textbook of Practical Organic Chemistry」B．S．ファーニスらによる編集、ロングマングループリミテッド、英国エセックス、１９８６及び「The peptides：Analysis, Synthesis, Biology」E．グラスらによる編集、アカデミックプレス、米国ニューヨーク州ニューヨーク、１９７９～１９８７、１～９巻のような標準的教科書に見られる。特に説明すると、式１の化合物は、下記工程：（ａ）式２

【００１５】

【化７】

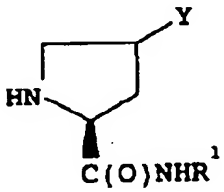


2

（式中、Ｘは、上記定義の通りである）のエポキシドと、式３

【００１６】

【化８】

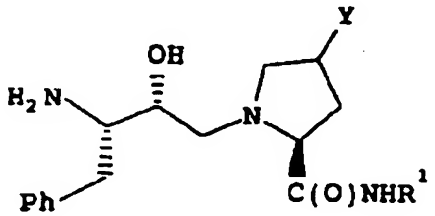


3

（式中、R^1 及びＹは、上記定義の通りである）のピロリジンカルボキサミドとを反応させて、式１（式中、Ｘ、R^1 及びＹは、上記定義の通りであり、Ｂは存在しない）の対応する化合物を得るか；または（ｂ）式４

【００１７】

【化９】



4

【００１８】（式中、R^1 及びＹは、上記定義の通りである）の化合物と、カルボン酸Ｘ－ＯＨ（式中、Ｘは、上記定義のR^2 Ｃ（Ｏ）または$R^{2'}OCH_2$ Ｃ（Ｏ）である）の反応性誘導体とを反応させて、式１（式中、Ｘは上記定義のR^2 Ｃ（Ｏ）または$R^{2'}OCH_2$ Ｃ（Ｏ）であり、R^1 及びＹは上記定義の通りであり、Ｂは存在しない）の対応する化合物を得るか；または（ｃ）式４（式中、R^1 及びＹは、上記定義の通りである）の化合物と、式Ｘ－ＮＨＣＨＲ^4 ＣＯＯＨ（式中、Ｘ及びR^4

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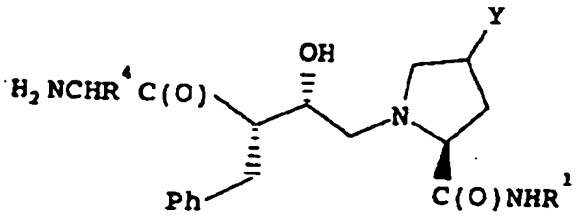
は、上記定義の通りである）のα－アミノ酸とを、カップリング剤の存在下でカップリングして、式１（式中、Ｘ、R^1 及びＹは、上記定義の通りであり、Ｂは、２価の基－ＮＨＣＨＲ^4 Ｃ（Ｏ）－である（式中、R^4 は上記定義の通りである））の対応する化合物を得るか；または（ｄ）式５

【００１９】

【化１０】



5

【００２０】（式中、R^1 、R^4 及びＹは、上記定義の通りである）の化合物と、カルボン酸Ｘ－ＯＨ（式中、Ｘは、上記定義のR^2 Ｃ（Ｏ）または$R^{2'}OCH_2$ Ｃ（Ｏ）である）の反応性誘導体とを反応させて、式１（Ｘは、R^2 Ｃ（Ｏ）または$R^{2'}OCH_2$ Ｃ（Ｏ）であり、R^1 及びＹは、上記定義の通りであり、Ｂは２価の基－ＮＨＣＨＲ^4 Ｃ（Ｏ）－である（式中、R^4 は上記定義の通りである））を得て；次いで、（ｅ）所望により、上記のセクション（ａ）、（ｂ）、（ｃ）または（ｄ）において得られた式１の化合物を、対応する治療学的に許容され得る酸付加塩に変換することにより製造されることができる。式１（式中Ｘは、通常使用されるＮ－保護基、例えば、Boc 、Ｚ、Fmocまたはｐ－メトキシベンジルオキシカルボニルである）の化合物の種は、工程（ａ）及び（Ｃ）により最も容易に及び好都合に得られる。この種は容易に利用しやすいので、個々の工程（ｂ）及び（ｄ）を経て式１（式中Ｘは、通常使用されるＮ－保護基以外である）の個々の化合物を製造する好適な経路のための中間体として有用である。従って、中間体として、この種の式１の化合物は、脱保護され（即ち保護基が除去される）、次いで得られたＮ末端遊離アミンは、式１（式中Ｘは、通常使用されるＮ－保護基、例えば、２－ピリジニルメトキシカルボニルまたは２－キノリニルカルボニル以外である）の化合物の最終的な製造のための、Ｂが存在しないかまたは存在するかによって工程（ｂ）及び（ｄ）に従って、それぞれ式４または式５の化合物として使用される。

【００２１】より明瞭にするために、上記工程（ａ）に従って、式１（式中、Ｂは存在しない）の化合物は、エポキシド２をピロリジンカルボキサミド３に添加することを含むＮ－アルキル化反応により製造されることができる。この反応は、２０～１１０℃の温度において、上記の２つの反応物質を、不活性溶媒、例えばエタノール、テトラヒドロフランまたはジメチルホルムアミド中

に接触状態で入れることによって好都合に実施されることができる。反応時間は、温度及び反応物質の特性に左右されるが、一般的な範囲は２～２４時間である。工程（ｂ）により、式１（式中、Ｂは存在せず、Ｘは上記定義のR² Ｃ（Ｏ）またはR²ＯＣＨ₂ Ｃ（Ｏ）である）の化合物は、式４の対応する化合物と、カルボン酸Ｘ－ＯＨ（式中、Ｘはそれぞれ上記定義のR² Ｃ（Ｏ）またはR²ＯＣＨ₂ Ｃ（Ｏ）である）の反応性誘導体とを反応させることによってそれぞれ得られる。適当な反応性誘導体は、適当なアシル基Ｘ－ＣＯを提供することができるアシル化剤であり、対応する酸ハロゲン化物、好適には塩化物または臭化物、活性エステル、無水物または混合された無水物を包含する。この反応は、知られた方法及び反応物質の適当な比率を選ぶことにより、または意図する反応基と競合するいずれか他の反応基のために、所望により知られた保護基を臨時に与えることにより、反応物質へ所望の選択性を与える手段を含む反応を実施するための条件に従って行われる。一般的には、この反応は、不活性溶媒、例えばテトラヒドロフラン、ジメチルホルムアミドまたはメチレンジクロライド中で、０～５０℃の温度において１５分～２４時間の範囲の反応時間行われる。

【００２２】工程（ｃ）によれば、式１（式中Ｂは、２価の基－ＮＨＣＨＲ⁴ Ｃ（Ｏ）－である（式中、Ｒ⁴ は、上記定義の通りである））の化合物は、カップリング剤の存在下で、式４の化合物と式Ｘ－ＮＨＣＨＲ⁴ ＣＯＯＨのα－アミノ酸とをカップリングすることによって得ることができる。カップリング剤を使用して、１の反応物質の遊離カルボキシルとその他の反応物質の遊離アミノ基との脱水カップリングを促進することはよく知られている；例えば、上記の「The Peptides：Analysis, Synthesis, Biology」第１～８巻参照。適当なカップリング剤の例としては、１，１’－カルボニル－ジイミダゾールまたはＮ，Ｎ’－ジシロロヘキシル－カルボジイミドがある。その他の例としては、Ｎ，Ｎ－ジシクロヘキシルカルボジイミドまたはＮ－エチル－Ｎ’－［（３－ジメチル－アミノ）プロピル］カルボジイミドの存在下での１－ヒドロキシベンゾトリアゾールがある。非常に実用的で有用なカップリング剤は、それ単独または１－ヒドロキシベンゾトリアゾールの存在下で使用される商業的に入手可能な（ベンゾトリアゾール－１－イルオキシ）トリス－（ジメチルアミノ）ホスホニウム　ヘキサフルオロホスフェートである。その他の非常に実用的で有用なカップリング剤は、商業的に入手可能な２－（１Ｈ－ベンゾトリアゾール－１－イル）－Ｎ，Ｎ，Ｎ’Ｎ’－テトラメチルウロニウム　テトラフルオロボレートである。カップリング反応は、メチレンジクロライド、アセトニトリルまたはジメチルホルムアミドのような不活性溶媒中で行われる。ジイソプロピルエチルアミンまたはＮ－メチルモルホリンのような過剰の有機アミンを添加して、反応混合物を約pH8に維持する。反応温度は、通常－２０～約３０℃の範囲であり、反応時間は１５分間から８時間である。

【００２３】工程（ｄ）を参照すると、この工程は、出発物質として式４の化合物の代りに式５の化合物を使用することのみを除けば、工程（ｂ）について上記した方法と同じ方法により行われる。工程（ａ）において出発物質として使用される式２のエポキシドは、知られたものであるか、または知られた方法により製造されることができる。特に詳しく言うと、式２のエポキシドは、１９８９年１２月２０日発行のＢ．Ｋ．ハンダらによる欧州特許出願第３４６，８４７号に記載されたものであるか、または上記特許出願中に記載された方法によって製造することができる。これらの工程におけるその他の出発物質、即ち、式３のピロリジンカルボキサミド及び式４及び５の化合物は、新規であり、従って、本発明の対象である。式４及び５の化合物の製造のための好適な方法は、既に上記に説明した。式３のピロリジンカルボキサミドは、知られた対応するピロリジンカルボン酸の標準アミド化によって製造されることができる。代替的には、それらは、Ｆ．ソウシー、Ｄ.ウェルニック及びP.ビューリューによる「J.Chem. Soc.Perkins Trans.」１、２８８５（１９９１）の方法により製造することもできる。式５のピロリジンカルボキサミドの製造方法は、下記の例において説明する。

【００２４】本発明の式１の化合物は、治療学的に許容され得る酸付加塩の形態で得ることができる。このような塩の例としては、有機酸、例えば、酢酸、乳酸、コハク酸、安息香酸、サリチル酸、メタンスルホン酸またはｐ－トルエンスルホン酸、並びに、ポリマー酸、例えば、タンニン酸またはカルボキシメチルセルロース、及び無機酸、例えば、ハロゲン化水素酸、例えば塩酸、硫酸またはリン酸との塩がある。所望により、Ｒ．Ａ．ボイソナスらによる「Helv. Chim. Acta」、４３、１８４９（１９６０）により記載された方法により、適当なイオン交換樹脂によって処理することにより、特定の酸付加塩をその他の酸付加塩、例えば無毒性の薬学的に許容され得る塩に転化する。一般的には、式１のペプチドの治療学的に許容され得る塩は、ペプチド自体と生物学的に十分均等である。

生物学的観点

式１の化合物またはその治療学的に許容され得る塩のＨＩＶプロテアーゼ阻害特性及びＨＩＶ病原体に対する細胞保護効果は、生化学的、微生物学的及び生物学的方法により立証されることができる。式１の化合物またはその治療学的に許容され得る塩のＨＩＶプロテアーゼ阻害特性を立証するための特に有効な方法は、「組換え型ＨＩＶプロテアーゼＨＰＬＣアッセイ」である。この方法は、ＨＩＶポリタンパク質の知られたＨＩＶプロテアーゼ分割部位を含むアミノ酸配列を有するデカペプチド

（基質）のＨＩＶプロテアーゼにより試験化合物が酵素分割を阻害する能力に基づく；Ｈ．Ｇ．クラウスリッヒら、「Proc. Nat.Acad. Sci.USA.」８６、８０７（１９８９）参照。このアッセイについての詳細と式１の例示化合物により得られた結果を下記の例において開示する。

【００２５】式１の化合物及びその治療学的に許容され得る塩がＨＩＶ感染から細胞を保護する能力は、ヒトＴ４セルラインのＨＩＶの細胞病原性に対する試験化合物の阻害効果を評価する微生物学的方法により立証されることができる。このような方法の典型例は、Ｓ．ハラダ及びＮ．ヤマモトによる「Jpn.J.Cancer Res.（Gann）」、７６、５４３（１９８５）及びＳ．ハラダらによる「Science」、２２９、５６３（１９８５）に記載されている。後者の方法に基づくアッセイを、下記の例において開示する。本発明の化合物またはその治療学的に許容され得る塩をヒトのＨＩＶ感染症を撃退するために使用した場合、このペプチドは１またはそれ以上の薬学的に許容され得る担体を含む賦形剤として、経口的、局所的または非経口的に投与されることができ、その割合はその化合物の溶解性、化学的性質、選ばれた投与経路及び標準生物学的慣行により決定される。経口投与のためには、前記化合物またはその治療学的に許容され得る塩は、薬学的に許容され得る担体中に、それぞれ約５～１５０mgの範囲の予め定められた量の活性成分を含むカプセルまたは錠剤のような単位投与形態物に処方されることができる。局所投与のためには、前記化合物は、活性剤を０．０１～２％、好ましくは０．０５～１％含む薬学的に許容され得る賦形剤に処方されることができる。これらの処方物は、クリーム、ローション、舌下錠または好ましくは経皮性パッチもしくは頬パッチの形態とすることができる。非経口投与のためには、式１の化合物は薬学的に許容され得る賦形剤または担体との組成物として、静脈内、皮下または筋内注射することにより投与される。注射による投与のためには、前記化合物を、溶液を等張性にするために十分量の薬学的に許容され得る塩またはグルコースの他に緩衝剤または保存剤のようなその他の溶質をも含むことができる滅菌水性賦形剤中の溶液中で使用することが望ましい。

【００２６】上記の処方物のための適当な賦形剤または担体は、標準の薬学教科書、例えば、「Remington's Pharmaceutical Sciences」、第１８版、マックパブリシングカンパニー、米国ペンシルバニア州イーストン、１９９０中に見ることができる。化合物の投与量は、投与形態物及び選ばれた特定の活性剤によって変化する。さらに、それは、治療下にある特定の宿主によって変化する。一般的には、治療は、ペプチドの最適投与量よりも実質的に少ない少投与量により開始される。その後、投与量は、その環境下において最適効果が得られるまで少しずつ増量することによって増加される。一般的に、本化合物は、有害なまたは心身に有害ないかなる副作用も起こさずに、抗ウィルス性の効果を一般的に得る濃度基準において投与されることが最も望ましい。経口投与のために、本化合物またはその治療学的に許容され得る塩は、１日当り体重１kgについて５～１５０mgの範囲、好ましくは体重１kgについて５～５０mgの範囲で投与される。全身性投与に関連して、式１の化合物は、上記の変量もあるが、体重１kg当り１０μg～１０００μgの投与量で投与される。上記に記載した処方物は、ＨＩＶ感染症の治療のための有効で比較的安全な医薬であるが、これらの処方物とその他の抗ウィルス性医薬または剤との可能な協働投与は排除されない。このようなその他の抗ウィルス性の医薬または剤は、可溶性ＣＤ４、ジドブジン、ジダノシン、ザルシタビン、ホスホノホルメート三ナトリウム、リババリン、アシクロビルまたは抗ウィルス性インターフェロン（例えば、α－インターフェロンまたはインターロイキン－２）を包含する。

【００２７】

【実施例】以下、実施例により本発明をさらに詳しく説明する。溶液の百分率または比率は、特に断らない限り、容量対容量の関係を示す。温度は、摂氏で示される。プロトン核磁気共鳴（ＮＭＲ）スペクトルは、ブルカー２００MHz スペクトロメーター上に記録した；化学的偏移（δ）は、ppm で報告される。実施例中において使用された略語は、Boc ：tert- ブチルオキシカルボニル；BOP ：（ベンゾトリアゾール－１－イルオキシ）トリス（ジメチルアミノ）ホスホニウムヘキサフルオロホスフェート；Bu^t ：tert- ブチル；Bzl ：ベンジル；DIEA：ジイソプロピルエチルアミン；DMF ：ジメチルホルムアミド；HEPES ：Ｎ－２－ヒドロキシエチル－ピペラジン－Ｎ’－２－エタンスルホン酸；Et_2O：ジエチルエーテル；EtOAc ：酢酸エチル；EtOH：エタノール；HPLC：高性能液体クロマトグラフィー；MeOH：メタノール；Ph：フェニル；THF ：テトラヒドロフラン；Ｚ：ベンジルオキシカルボニルを包含する。

【００２８】実施例１

４（Ｓ）－ベンジルオキシ－Ｎ－tert－ブチル－１－（tert－ブチルオキシカルボニル）ピロリジン－２（Ｓ）－カルボキサミドの製造

（ａ）Ｎ－保護された酸、１－（tert－ブチルオキシカルボニル）－４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸を、ＴＨＦ／H_2O（１：１）溶液中で過剰のＮａＯＨの存在下で、室温において１８時間、４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸｛シス－４－ヒドロキシ－Ｌ－プロリン、Ｓ．Ｇ．ラマスワミ及びＥ．アダムズによる「Ｊ．Org．Chem.」、４２、３４４０（１９７７）に記載｝とジ－tert－ブチルカルボネートとを反応させることによって製造した。（ｂ）このようにして得られたＮ－保護された酸（４００mg、1.73mmol）をＤＭＦ（７ml）中に溶解し

た。水素化ナトリウム（９９%、８７mg、3.63mmol）をこの溶液に添加した。得られた混合物を室温（２０～２２℃）において２時間撹拌した。臭化ベンジル（1.03ml、8.65mmol）を添加し、得られた混合物を室温において１８時間撹拌した。その後、この混合物をEtOAcにより希釈し、０℃に冷却して、１０%水性クエン酸を添加することによって酸性（pH3）とした。有機層を分離し、H_2O及び食塩水により洗浄し、乾燥し（$MgSO_4$）、減圧下で濃縮乾固した。残存した黄色油状物をクロマトグラフィー（SiO_2、溶離液：ヘキサン－EtOAc、９：１）により精製し、４（Ｓ）－ベンジルオキシ－１－（tert－ブチルオキシカルボニル）ピロリジン－２（Ｓ）－カルボン酸ベンジルエステル（３０１mg、７０%）を得た。

【００２９】（Ｃ）後者の化合物（３０１mg、0.73mmol）をMeOH/H_2O（２：１、４ml）中に溶解した。得られた溶液を撹拌し、０℃に冷却した。NaOHの水性２M溶液（1.16ml）を添加した。１０分後に、この混合物を室温に加温して、同じ温度において１８時間撹拌した。その後、反応体をEt_2O/ヘキサン（１：１、１０ml）及びH_2O（５ml）により希釈した。水性層を分離し、Et_2O/ヘキサン（１：１）により２回抽出し、０℃に冷却し、１０%水性クエン酸により酸性とし（pH3）、EtOAc（３X）により抽出した。合わせたEtOAc抽出物をH_2O（２X）及び食塩水により洗浄し、乾燥し（$MgSO_4$）、減圧下で濃縮した。残存物を高真空下で乾燥し、量的収量の４（Ｓ）－ベンジルオキシ－１－（tert－ブチルオキシカルボニル）－ピロリジン－２（Ｓ）－カルボン酸を得た。（ｄ）CH_2Cl_2中の後者の化合物（234.7mg、0.73mmol）の0.2 Mの溶液に、ＤＩＥＡ（127μl、0.73mmol）を添加し、次いで、tert-ブチルアミン（84.4μl、0.803mmol）及びＢＯＰ（387mg、0.876mmol）を添加した。この反応混合物を、周期的検査により及び必要に応じてＤＩＥＡを添加することによってそのpHを８に維持しながら、室温において３時間撹拌した。その後、反応混合物をEtOAcにより希釈し、$NaHCO_3$の飽和水溶液（２X）、H_2O及び食塩水により連続して洗浄した。有機層を乾燥し（$MgSO_4$）、減圧下で濃縮乾固した。得られた黄色の油状物をフラッシュクロマトグラフィー（SiO_2、溶離液：ヘキサン－EtOAc、７：３その後６：４）により精製し、標記化合物を得た（252mg、９２%）。^{1}NMR（$CDCl_3$）δ7.40-7.25（m、５H）、6.05（広幅s、１H）、4.6-4.35（広幅d、２H）、4.2-4.05（m、２H）、3.8-3.55（m、２H）2.55-2.1（m、２H）1.46（s、９H）、1.20（広幅s、９H）。

【００３０】実施例２

１－｛３（Ｓ）－アミノ－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｓ）－ベンジルオキシ－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式４：R^1＝Ｃ（CH_3）$_3$及びＹ＝OCH_2Ph；Ｃ（Ｏ）NHR_1／Ｙ＝シス）の製造

（ａ）６NHCl／ジオキサン中の式１の標記化合物（250mg、0.664mmol）の溶液を室温において２０分間撹拌し、次いで減圧下で濃縮乾固した。残存物をEtOAc（１０ml）及び２N水性NaOH（３ml）により希釈した。得られた混合物を室温において１５分間撹拌した。有機層を分離し、最小量のH_2O及び食塩水により洗浄し、乾燥し（$MgSO_4$）、減圧下で濃縮乾固した。残存物を高真空下で乾燥し、４（Ｓ）－ベンジルオキシ－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド、式３（式中、R1はＣ（CH_3）$_3$及びＹはOCH_2Ph{Ｃ（Ｏ）NHR^2／Ｙ＝シス}である）のカルボキサミドを得た。（ｂ）後者の化合物を、無水EtOH（５ml）中で、３（Ｓ）－（ベンジルオキシカルボニル）－１、２（Ｒ）－エポキシ－４－フェニルブタン（180mg、0.604mmol）、即ち式２（式中、XはZ）と混合した。上記Ｂ．Ｋ．ハンダら参照。この混合物を還流下で１８時間加熱し、次いで減圧下で濃縮乾固した。残存物をフラッシュクロマトグラフィー（SiO_2、溶離液：$CHCl_3$－MeOH、３９：１その後１９：１）により精製し、４（Ｓ）－ベンジルオキシ－１－｛３（Ｓ）－｛（ベンジル－オキシカルボニル）アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（220mg、６３%）を白色の泡状物として得た。

（ｃ）後者の化合物（220mg、0.384mmol）を水素添加分解（５%M、Ｐｄ／Ｃ、$H_2$１気圧、MeOH、3.5時間）に付して、標記の化合物を得て、すぐに下記実施例のカップリング操作に従って用いた。

【００３１】実施例３

４（Ｓ）－ベンジルオキシ－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式１：X＝Z、Ｂ＝Val、R^1＝Ｃ（CH_3）$_3$及びＹ＝OCH_2Ph；Ｃ（Ｏ）NHR^1／Ｙ＝シス）の製造

標記化合物を、下記のカップリング方法に従って製造した：ＤＩＥＡ（33.4μl、0.192mmol）、保護されたアミノ酸Z-Val-OH（53.1mg、0.211mmol）及びＢＯＰ（102mg、0.23mmol）を、CH_2Cl_2中の実施例２の標記化合物の0.2 M溶液（0.192mmol）に添加した。この反応混合物を、室温において２時間撹拌しながら、周期的検査及び必要に応じてＤＩＥＡを添加することによってpH8に維持した。その後、この反応混合物を、EtOAcにより希釈し、NaHCO3の飽和水溶液（２X）、H_2O及び食塩水により連続的に洗浄した。有機層を乾燥し（$MgSO_4$）、減圧下で濃縮した。残存物をフラッシュクロマトグラフィー（SiO_2、溶離液：$CHCl_3$－MeOH、３９：１）により精製し、本実施例の標記化合物を白色の固形物として得た（108mg、８３%）。ＦＡＢマススペクトル、ｍ／ｚ：

673.3（M＋H）⁺。

【００３２】実施例４

４（Ｒ）－ベンジルオキシ－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式１：Ｘ＝Ｚ、Ｂ＝Val、R^1＝Ｃ（CH_3）$_3$及びＹ＝OCH_2Ph；Ｃ（Ｏ）NHR^1／Ｙ＝トランス）の製造

実施例１のセクション（ａ）において４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸の代りに、等量の４（Ｒ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸（トランス－４－ヒドロキシプロリン－２－カルボン酸）、上記Ｓ．Ｇ．ラマスワミ及びＥ．アダムズ参照、を使用すること以外は、実施例１、２及び３の手順に連続的に従って、標記化合物を得た。ＦＡＢマススペクトル、ｍ／ｚ：673.3（Ｍ＋Ｈ）⁺。

【００３３】実施例５

４（Ｒ）－ベンジルオキシ－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式１：Ｘ＝Ｚ、Ｂ＝Asn、R^1＝Ｃ（CH_3）$_3$及びＹ＝OCH_2Ph；Ｃ（Ｏ）NHR^1／Ｙ＝トランス）の製造

実施例１のセクション（ａ）において４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸の代りに、等量の４（Ｒ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸を使用すること以外は、実施例１及び２の手順に連続的に従って、及びこのようにして得られた１－｛３（Ｓ）－アミノ－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－ベンジルオキシ－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミドを下記のカップリング工程に付して、標記化合物を得た。

【００３４】１－ヒドロキシベンゾトリアゾール（20.1mg、0.148mmol）をＴＨＦ（２ml）中のＮ、Ｎ’－ジシクロヘキシルカルボジイミド（34mg、0.165mmol）の冷却された（０℃）溶液へ添加した。この混合物を１５分間撹拌した。ＤＭＦ（１ml）中の保護されたアミノ酸Z-Asn-OH（395mg、0.148mmol）の溶液及びＤＭＦ（１ml）中の上記した１－｛３（Ｓ）－アミノ－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－ベンジルオキシ－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（35.4mg、0.083mmol）をこの混合物へ添加した。得られた混合物を室温までゆっくりと加温し、次いで１８時間撹拌した。その後、この混合物をEtOAcにより希釈した。有機層を分離し、$NaHCO_3$の飽和水溶液、H_2O及び食塩水により洗浄し、乾燥し（$MgSO_4$）、減圧下で濃縮乾固した。白色の固形残存物をフラッシュクロマトグラフィー（SiO_2、溶離液：EtOAc／MeOH、９７：３その後１９：１）により精製し、本実施例の標記化合物を得た。ＥＩマススペクトル、ｍ／ｅ：389.2（Ｍ＋２Ｈ）⁺。

（Ｎ、Ｎ’－ジシクロヘキシルカルボジイミドの存在下で１－ヒドロキシベンゾトリアゾールを使用する上記に例示したカップリング方法は、式１（式中Ｂはアミノ酸残基Asnを示す）の化合物の製造のための好適なカップリング方法を示すことに注意されたい。）

【００３５】実施例６

４（Ｓ）－ベンジルオキシ－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式１：Ｘ＝Ｚ、Ｂ＝Asn、R^1＝Ｃ（CH_3）$_3$及びＹ＝OCH_2Ph；Ｃ（Ｏ）NHR^1／Ｙ＝シス）の製造

実施例１及び２の手順及び実施例５のカップリング方法に連続的に従って、標記化合物を得た。ＦＡＢマススペクトル、ｍ／ｚ：688.4（Ｍ＋Ｈ）⁺；710.4（Ｍ＋Ｎａ）⁺。

実施例７

１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）－バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチル－４（Ｓ）－（２－メチルプロピルオキシ）ピロリジン－２（Ｓ）－カルボキサミド｛式１：Ｘ＝Ｚ、Ｂ＝Val、R^1＝Ｃ（CH_3）$_3$及びＹ＝$OCH_2CH(CH_3)_2$；Ｃ（Ｏ）NHR^1／Ｙ＝シス｝の製造

実施例１のセクション（ｂ）の手順において、臭化ベンジルの代りに当量の２－メチルプロピルブロミドを使用すること以外は、実施例１、２及び３の手順に連続的に従って、標記化合物を得た。ＥＩマススペクトル、ｍ／ｅ：583.4（MH_2－C_4H_9）⁺。

【００３６】実施例８

１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）－バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチル－４（Ｒ）－（２－メチルプロポキシ）ピロリジン－２（Ｓ）－カルボキサミド｛式１：Ｘ＝Ｚ、Ｂ＝Val、R^1＝Ｃ（CH_3）$_3$及びＹ＝$OCH_2CH(CH_3)_2$；Ｃ（Ｏ）NHR^1／Ｙ＝トランス｝の製造

実施例１のセクション（ａ）の手順において４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸の代りに等量の４（Ｒ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸を用い、実施例１のセクション（ｂ）において臭化ベンジルの代りに等量の２－メチルプロピルブロミドを用いること以外は、実施例１、２及び３の手順に連続的に従って、標記化合物を得た。ＥＩマススペクトル、ｍ／ｅ：583.3（MH_2－C_4H_9）⁺。

【００３７】実施例９

４（Ｒ）－ベンジルオキシ－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－シクロプロピルピロリジン－２（Ｓ）－カルボキサミド（式

１：Ｘ＝Ｚ、Ｂ＝Val 、R^1 ＝シクロプロピル及びＹ＝OCH_2Ph；Ｃ（O)NHR^1／Ｙ＝トランス）の製造
実施例１のセクション（ａ）において４（Ｓ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸の代りに等量の４（Ｒ）－ヒドロキシピロリジン－２（Ｓ）－カルボン酸、実施例１のセクション（ｄ）においてtert－ブチルアミンの代りに当量のシクロピロピルアミンを使用すること以外は、実施例１、２及び３の手順に連続的に従って、標記化合物を得た。ＥＩマススペクトル、ｍ／ｅ：657.5 （Ｍ＋Ｈ）$^+$。

実施例１０

４－ベンジル－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）－アスパラギニル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミド（式１：Ｘ＝Ｚ、Ｂ＝Asn 、R^1 ＝Ｃ（CH_3)$_3$ 及びＹ＝Bzl）の４（Ｒ、Ｓ）、４（Ｒ）及び４（Ｓ）異性体の製造

【００３８】上記Ｆ．ソウシー、Ｄ．ウェルニック及びＰ．ビューリューにより記載された方法を応用して、４－ベンジル－１－（tert－ブチルオキシカルボニル）ピロリジン－２（Ｓ）－カルボン酸の４（Ｒ）及び４（Ｓ）ジアステレオマーの混合物（３：２、ｗ／w)を、セリンラクトン及び３－フェニル－２－ブロペニルブロミドから得た。BOP の存在下でのジアステレオマー混合物とtert－ブチルアミンとの実施例１のセクション（ｄ）の方法によるカップリングにより、４－ベンジル－Ｎ－tert－ブチル－１－（tert－ブチルオキシ－カルボニル）ピロリジン－２（Ｓ）－カルボキサミドの４（Ｒ）及び４（Ｓ）異性体の対応するジアステレオマー混合物を得た。その後、実施例２のセクション（ｂ）の手順及び式３のカルボキサミドとして後者のジアステレオマー混合物を使用することによって、４－ベンジル－１－｛３（Ｓ）－｛（ベンジルオキシカルボニル）－アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミドの４（Ｒ）及び４（Ｓ）異性体の対応するジアステレオマー混合物を得た。ＦＡＢマススペクトル、ｍ／ｚ：558 （Ｍ＋Ｈ）$^+$。また、後者のジアステレオマーの混合物とＮ－保護されたアミノ酸Z-Asn-OHとの実施例５のカップリング方法による反応によって、４－ベンジル－１－｛３（Ｓ）－｛｛Ｎ－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－Ｎ－tert－ブチルピロリジン－２（Ｓ）－カルボキサミドの４Ｒ及び４Ｓ異性体の対応するジアステレオマー混合物を得た。ＦＡＢマススペクトル、ｍ／ｚ：672 （Ｍ＋Ｈ）$^+$。

【００３９】この２つの異性体をＨＰＬＣ技術により分離し、対応する純粋な４Ｒ及び４Ｓ異性体を得た。詳しく説明すると、５０％水性酢酸（最初の状態）2.5ml 中に溶解された最後に記載した混合物の20mlの試料を、ワットマンマグナム９（登録商標）、C_{18}オクタデシルシリルカラム（0.94×50cm）上に充填した。初期のカラム平衡条件は下記の通りである：１０％Ａ及び９０％Ｂ（ポンプＡ：アセトニトリル中0.06％トリフルオロ酢酸；ポンプＢ：H_2O 中0.06％トリフルオロ酢酸）。一度酢酸に対応するピーク（溶媒の正面）を通過すると、線状勾配が続いた。異性体の分離プログラムは下記の通りであった：１０～３０％Ａ５分間、３０％Ａ１０分間、その後３０～１００％Ａ１１０分間、3ml／分及び２３０nm。４（Ｒ）異性体及び４（Ｓ）異性体をそれぞれ６０％Ａ（9.2mg)及び６３％Ａ（8.3mg)において収集した。

【００４０】実施例１１

Ｎ－tert－ブチル－１－｛２（Ｒ）－ヒドロキシ－４－フェニル－３（Ｓ）－｛｛Ｎ－２－キノリルカルボニル）バリル｝アミノ｝－ブチル｝－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミド（式１：Ｘ＝２－キノリルカルボニル、Ｂ＝Val 、R^1 ＝Ｃ（CH_3)$_3$ 及びＹ＝２－ピリミジニルチオ）の製造

（ａ）Ｎ－保護された酸（17.5g 、75.6mmol 、実施例１のセクション（ａ）に記載）をCH_2Cl_2（３００ml）及びＤＩＥＡ（13ml、76.6mmol）中に溶解した。tert－ブチルアミン（8.73ml、83.1mmol）をこの溶液に添加し、次いで、BOP （40g、90.7mmol）及びDIEA（13ml、151mmol)を添加した。この混合物を室温において７時間撹拌し、次いでEtOAc により希釈した。有機層を分離し、$NaHCO_3$の飽和水溶液（２Ｘ）、H_2O （２Ｘ）及び食塩水（２Ｘ）により洗浄し、乾燥し（$MgSO_4$）、蒸発乾固した。得られた固形残存物をEt_2O／EtOAc （９：１）により摩砕し、濾紙上で集め、Et_2Oにより洗浄し乾燥して、Ｎ－tert－ブチル－１－（tert－ブチルオキシカルボニル）－４（Ｒ）－ヒドロキシピロリジン－２（Ｓ）－カルボキサミド（15.6g 、72%）を得た。

【００４１】（ｂ）後者の化合物（5.0g、17.5mmol）をトルエン／ＴＨＦ（３：１、175ml)中に溶解した。トリフェニルホスフィン（5.72g 、21.8mmol）及びイミダゾール（1.08g 、30.5mmol）を室温においてその溶液に添加した。得られた混合物を４５～５０℃に加温した。ヨー素（5.54g 、21.8mmol）を添加して、得られた混合物を８０分間４５～５０℃において激しく撹拌した。その後、この反応混合物を冷却して、Et_2O及びH_2O により希釈した。有機層を分離し、$NaHCO_3$の飽和水溶液（１Ｘ）及び食塩水（１Ｘ）により洗浄し、乾燥し（$MgSO_4$)蒸発乾固して、いくらかの固形物（酸化トリフェニルホスフィン）を含む茶色の油状物を得た。この油状固形物をEt_2Oにより摩砕し、固形物を濾紙上に集めた。濾液を蒸発乾固して、茶色の油状物を得た。この油状物をフラッシュクロマトグラフィー（SiO_2、溶離液：EtOAc ／ヘキサン、１：４）により精製し、Ｎ－tert－ブチル－１－（tert－ブチルオキシカルボニル）－４（Ｓ）－ヨード

ピロリジン－２（Ｓ）－カルボキサミドを、黄色の固形物として得た（4.83g、７０％）。^{1}ＮＭＲ（$CDCl_3$）δ 6.2-6.0（広幅ｓ、１Ｈ）、4.27-4.0（ｍ、３Ｈ）、3.75-3.55(m、１Ｈ）、2.9-2.5（ｍ、２Ｈ）、1.47（ｓ、９Ｈ）、1.38（ｓ、９Ｈ）。

【００４２】（ｃ）２－ピリミジンチオール（1.06g、9.46mmol）をＤＭＦ（10ml）中の水素化ナトリウム（９９％、182mg、7.57mmol）の冷却された（０℃）懸濁液へ１滴ずつ添加した。この混合物を同じ温度で３０分間撹拌した。その後、ＤＭＦ（５ml）中の上記セクション（ｂ）の生成物（1.5g、3.79mmol）の溶液を、この混合物へ１滴ずつ添加した。この反応混合物を室温において１８時間撹拌し、次いで、EtOAc 及びH_2O により希釈した。有機層を分離し、冷H_2O（１Ｘ）、NaOHの１Ｎ水性溶液（２Ｘ）及び食塩水（１Ｘ）により洗浄し、乾燥し（$MgSO_4$）及び蒸発乾固して、固形物を得た。この固形物をEt_2Oにより摩砕したところ、Ｎ－tert－ブチル－１－（tert－ブチルオキシカルボニル）－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミドをオフホワイトの固形物として得た。^{1}ＮＭＲ（$CDCl_3$）δ8.53-8.51(d、Ｊ＝4.85Hz、２Ｈ）、7.01-6.96（ｔ、Ｊ＝4.85、10.0Hz、１Ｈ）、5.97-5.75(広幅ｓ、１Ｈ）、4.4-4.2(m、２Ｈ）、4.1-3.91（ｍ、１Ｈ）、3.70-3.35(m、２Ｈ）、2.92-2.75(m、１Ｈ）、1.47（ｓ、９Ｈ）、1.36（ｓ、９Ｈ）。ＦＡＢマススペクトル（ｍ／ｚ）：381(Ｍ＋Ｈ)$^+$、403（Ｍ＋Ｎａ)$^+$。

（ｄ）後者の化合物を脱保護して、実施例２のセクション（ａ）及び（ｂ）の方法に従って、式2（式中、Ｘは Boc である）のエポキシドと反応させて、Ｎ－tert－ブチル－１－｛３（Ｓ）－｛（tert－ブチルオキシカルボニル）アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミドを得た。ＦＡＢマススペクトル、ｍ／ｚ：544(Ｍ＋Ｈ)$^+$、566(Ｍ＋Ｎａ)$^+$。または、後者の化合物を実施例２のセクション（ａ）の手順に従って脱保護し、実施例３の手順に従って、Boc-Val-OHとカップリングして、Ｎ－tert－ブチル－１－｛３（Ｓ）－｛｛Ｎ－（tert－ブチルオキシカルボニル）バリル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミドを得た。ＦＡＢマススペクトル（ｍ／ｚ）：643(Ｍ＋Ｈ)$^+$、665(Ｍ＋Ｎａ)$^+$。

【００４３】（ｅ）６NのHCl ／ジオキサン（７ml）中の後者の化合物（887mg、1.38mmol）の溶液を室温において２０分間撹拌した。この溶媒を減圧下で除去した。白色固形物の残存物を高真空下において２０分間乾燥して、対応する脱保護されたアミンを塩酸塩として得た。後者の塩をCH_2Cl_2（７ml）及びDIEA（481 μl、2.76mmol）中に溶解した。２－キノリンカルボン酸（263ml、1.52mmol）及びＢＯＰ（732mg、1.66mmol）をこの塩の溶液に添加した。この反応混合物のpHを、周期的な検査とＤＩＥＡを必要により添加することによって８に維持しながら、室温において５時間撹拌した。その後、この反応混合物をEtOAc により希釈し、$NaHCO_3$の飽和水溶液（２Ｘ）、H2O(２Ｘ）及び食塩水により連続的に洗浄した。有機層を乾燥し（$MgSO_4$）、減圧下で濃縮乾固した。得られた無色の油状物をフラッシュクロマトグラフィー（SiO_2、溶離液：ヘキサン－EtOAc、３：７及びその後１：９）により精製して、標記化合物を白色の泡状物（750mg、７８％）として得た。この泡状物をEt_2Oにより摩砕したところ、標記化合物が白色の固形物として得られた（378mg、４０％）。ＦＡＢマススペクトル、ｍ／ｚ：698(Ｍ＋Ｈ)$^+$、720(Ｍ＋Ｎａ)$^+$。この化合物のＮＭＲは、指定された構造と同じであった。セクション（ｃ）において２－ピリミジンチオールの代りに３－ピリジンメタンチオールを使用すること以外は、本実施例の手順に従って、Ｎ－tert－ブチル－１－｛２（Ｒ）－ヒドロキシ－４－フェニル－３（Ｓ）－｛｛Ｎ－（２－キノリニルカルボニル）バリル｝－アミノ｝ブチル｝－４（Ｒ）－｛（３－ピリジニルメチル）チオ｝ピロリジン－２（Ｓ）－カルボキサミドを得る。ＦＡＢマススペクトル、ｍ／ｚ：711(Ｍ＋Ｈ)$^+$、733(Ｍ＋Ｎａ)$^+$。再び、セクション（ｃ）において２－ピリミジンチオールの代りに、２、６－ジメチル－４－ヒドロキシピリミジンを使用すること以外は本実施例の手順に従って、Ｎ－tert－ブチル－１－｛２（Ｒ）－ヒドロキシ－４－フェニル－３（Ｓ）－｛｛Ｎ－（２－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－４（Ｒ）－｛（２、６－ジメチル－４－ピリミジニル）オキシ｝ピロリジン－２（Ｓ）－カルボキサミドを得る。ＦＡＢマススペクトル、ｍ／ｚ：710(Ｍ＋Ｈ)、586（Ｍ＋Ｈ－$C_6H_8N_2O$)+。

【００４４】実施例１２

Ｎ－tert－ブチル－１－｛３（Ｓ）－｛｛（２、６－ジメチルフェノキシ）アセチル｝アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミド（式１；Ｘ＝（２、６－ジメチル－フェノキシ）アセチル、Ｂは存在せずR^1＝C（CH_3)$_3$及びＹ＝２－ピリミジニルチオ）の製造

実施例１１のセクション（ｄ）において記載した、Ｎ－tert－ブチル－１－｛３（Ｓ）－｛Ｎ－（tert－ブチルオキシカルボニル）アミノ｝－２（Ｒ）－ヒドロキシ－４－フェニルブチル｝－４（Ｒ）－（２－ピリミジニルチオ）ピロリジン－２（Ｓ）－カルボキサミドを、通常の方法によりBoc 保護基を除去することによって、その対応する第一アミン、即ちＮ－tert－ブチル－１－（３（Ｓ）－アミノ－２（Ｒ）－ヒドロキシ－４－フェニルブチル）－４（Ｒ）－（２－ピリミジニルチオ）ピロリ

ジン－2－カルボキサミドに転化した。後者の化合物を実施例3の手順に従って、（2、6－ジメチルフェノキシ）酢酸とカップリングし、標記化合物を得た。ＦＡＢマススペクトル、m／z：606(M＋H)⁺、628(M＋Na)⁺。

【００４５】前記第一アミンの代りに対応する第一アミン、Ｎ－tert－ブチル－1－（3（Ｓ）－アミノ－2（Ｒ）－ヒドロキシ－4－フェニルブチル）－4（Ｒ）－｛（3－ピリジニルメチル）－チオ｝ピロリジン－2－カルボキサミド（実施例１１のＮ－tert－ブチル－1－｛2（Ｒ）－ヒドロキシ－4－フェニル－3（Ｓ）－｛｛Ｎ－（2－キノリニルカルボニル）バリル｝アミノ｝－ブチル｝－4（Ｒ）－｛（3－ピリジニルメチル）チオ｝ピロリジン－2（Ｓ）－カルボキサミドの中間体として使用された）を使用すること以外は、本実施例の手順に従って、Ｎ－tert－ブチル－1－｛3（Ｓ）－｛｛2、6－ジメチルフェノキシ）アセチル｝アミノ｝－2（Ｒ）－ヒドロキシ－4－フェニルブチル｝－4（Ｒ）－｛（3－ピリミジニルメチル）－チオ｝ピロリジン－2（Ｓ）－カルボキサミド、ＦＡＢマススペクトル、m／z：619(M＋H)⁺、641（M＋Na)⁺を得た。

【００４６】実施例１３

組換えＨＩＶプロテアーゼアッセイ：

酵素：ＨＩＶプロテアーゼを、下記の手順に従って、E.coli中で表現した｛構造物ｐＢＲＴ1prt⁺、W.G.ファーメリーら、「Science」、２３６、３０５（１９８７）参照｝：特に断らない限り、全ての溶液は水性溶液である。

(i)発酵

ｐＢＲＴ1prt⁺プラスミドを含むE.coli細胞を使用して、１００μg／mlのアンピシリンを含むルリアーベルタニブロスからなる接種培養基に接菌した。フラスコを１７時間激しく動かしながら３７℃においてインキュベートした。滅菌Ｍ９ブロスを含み１００μg／mlのアンピシリンを補給された生成フラスコに、上記の接種培養物を使用して1％（ｖ／ｖ）の濃度で接菌した。各生成フラスコ中の全容量は、２Ｌのエルレンマイヤーフラスコ中５００mlであった。光学濃度（λ＝540nm)0.6に対応する細胞濃度となるまで（希釈なし）、フラスコを激しく動かしながら３７℃においてインキュベートした。この時間の範囲は通常3～4時間である。次いでフラスコに5mMイソプロピルチオガラクトシド（ＩＰＴＧ、リサーチオーガニクス、米国オハイオ州クリーブランド）を補給し、細胞濃度が１６倍の希釈において光学濃度0.2となるまで、インキュベートを続けた。次いで、フラスコに1mMフェニルメチルスルホニルフルオリド（ＰＭＳＦ）を補給し、素速く4℃に冷蔵した。この細菌細胞を4℃における遠心分離により回収した。得られた湿潤ペレットを－７０℃において保存した。

【００４７】（ii）アッセイ等級の酵素の抽出及び製造

下記のすべての工程は特に断らない限り、4℃において行なわれた。凍結した細胞を緩衝液Ａ｛５０mMトリス（ヒドロキシメチル）アミノエタンHCl(トリス－HCl、pH7.4)；0.6mM エチレンジアミン四酢酸（ＥＤＴＡ）；0.375 MNaCl、0.2％NonidetP-40(登録商標)（ＢＤＨケミカルズリミテッド、英国プール）；1mMＰＭＳＦ｝と、細胞重量1部に対して緩衝液Ａ9部の割合で添加した。珪ソウ土（セライト５４５（登録商標）、ジョンマンビル、ロムポック、米国カリフォルニア州）を、湿潤細胞重量1部に対して2部の割合で添加した。得られたスラリーを8×15秒バルスでウェアリング（登録商標）工業用ブレンダー上で高速度（約20,000rpm)で均質化した。細胞の破片／セライト（登録商標）を遠心分離により収集し、得られたペレットを、湿潤固形物1部に対して緩衝液Ａ4.5部を用いて上記の均質化方法により抽出した。両均質化工程から得られた上清を合わせ、可溶性タンパク質を固形$(NH_4)_2SO_4$を添加することにより沈殿させて、最終濃度７５％飽和を得た。この混合物を６０分間激しく動かし、沈殿物を遠心分離により回収した。得られたペレットを緩衝液Ｂ｛５０mMトリス－HCl、pH8；３０mMNaCl；1mMＤＬ－ジチオトレイトール（ＤＴＴ）；1mMＥＤＴＡ；1mMＰＭＳＦ；１０％グリセロール｝中に懸濁し、同じ緩衝液に対して１８時間透析した。

【００４８】タンパク質１５０mgを含む透析された抽出物のアリコートを７０cm長の床寸法及び2.5cmの径を有するセファデックスＡ２５（登録商標）アニオン交換カラム（ファルマシア、スウェーデン国アップサラ）上に充填した。試料を線状流速１０cm／時間において緩衝液Ｂによりイソクラティックに溶離した。ＨＩＶプロテアーゼ活性を含む画分（下記のアッセイについての記載を参照）を合わせ、可溶性のタンパク質を、飽和水性$(NH_4)_2SO_4$を添加することにより沈殿し、全$(NH_4)_2SO_4$濃度８５％飽和を得た。沈殿したタンパク質を遠心分離により除去し、得られたペレットを緩衝液Ｃ｛５０mM2－（4－モルホリノ）エタンスルホン酸（ＭＥＳ）、pH5.5；１５０mMNaCl；1mMＤＴＴ；1mMＥＤＴＡ；１０％グリセロール｝中に溶解した。この沈殿を緩衝液Ｃに対して１８時間透析し、次いで－７０℃において凍結した。全粗抽出物を上記記載の方法と同じ方法により、タンパク質１５０mgを含むアリコートにしてクロマトグラフィーにより精製した。各バッチから得られた最終製造物を集め、３４μLのアリコートに分割し、－７０℃において保存した。２０Ｌの発酵から回収された最終タンパク質は、分割された基質／分／mgが18.2mmolのＨＩＶプロテアーゼの特異的活性を有し、典型的には３００mgであった。使用前に、アリコートを緩衝液（下記参照）により最初の濃度の１／３８に希釈した（即ち、酵素作用溶液）。

基質：ＶＳＦＮＦＰＱＩＴＬ－NH_2、MW1164（クラウスリッヒら、「Proc. Natl. Acad. Sci．USA」８６、８０７（１９８９）参照）を基質として使用した。この基質は、ＤＭＳＯ中のストック１０mMとし、４℃で保存した。使用前に、このストックを緩衝液で希釈し、溶液４００μＭを得た（即ち、基質作用溶液）。

【００４９】緩衝液：ＭＥＳ（100mM）、ＫＣｌ（300mM）及びＥＤＴＡ（５mM）を蒸留H_2O(90ml）中に溶解し、得られた溶液を濃水性NaOHにより5.5に調整した。後者の溶液をH_2Oにより希釈して１００mlとし、緩衝液を得た。

手順：（１）アッセイ混合物は、基質作用溶液２０μl、１０％ＤＭＳＯ中の試験化合物の溶液１０μl及び酵素作用溶液１０μlを混合することによって製造した。（２）このアッセイ混合物を３７℃において３０分間インキュベートした。（３）反応体を、２％水性トリフルオロ酢酸２００μlを添加することによって急冷した。（４）急冷されたアッセイ混合物１００μlを流速４ml／分における段階的勾配によるバーキン－エルマー３×３ＣＲＣ８カラム（バーキンエルマーインコーポレイテッド、米国コネティカット州ノーワーク）を使用するＨＰＬＣに付することによって、基質及び生成物（即ち、ＶＳＦＮＦ及びＰＱＩＴＬ－NH_2）を分離した。この勾配は下記の通りである：

0.0–0.5分、７０％Ａ／３０％Ｂ；
0.5–3.0分、６７％Ａ／３３％Ｂ；
3.0–5.0分、２０％Ａ／８０％Ｂ；
＊5.0–6.5分、７０％Ａ／３０％Ｂ；

（上記ＡはH_2O中の３mM硫酸ドデシルナトリウム／0.05％H_3PO_4であり、Ｂはアセトニトリル中0.05％H_3PO_4である）。溶離は２１０nmにおいて監視した。（５）試験化合物なしのアッセイ混合物である対照を工程２～４に同時に付した。

【００５０】阻害の考察：分割生成物及び残存の親基質をピークの高さまたは適当なＨＰＬＣピークの積分により定量した。基質転化は下記の関係式を使用して算出した：

転化（％）＝（生成物のピーク高さまたはピーク面積の合計／基質及び生成物のピーク高さまたはピーク面積の合計）×１００

試験化合物の酵素阻害は、下記のようにして算出した。

阻害（％）＝１００－（アッセイ混合物の転化（％）／対照の転化（％））×１００

ＨＩＶ－プロテアーゼの５０％阻害をもたらす試験化合物の濃度、即ち、IC_{50}は、下記のようにして測定した：酵素の阻害百分率を、試験化合物の３つの異なる濃度の最小について測定した。その後、IC_{50}を、試験化合物の濃度に対する酵素の阻害百分率をプロットすることによりグラフ上で決定した。　組換えＨＩＶプロテアーゼＨＰＬＣアッセイにおいて測定された、式１の例示化合物のIC_{50}を下記の表中に掲げる。

【００５１】

【表１】

表１

番号	化合物	IC_{50}（nM）
1	4（S）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	１５０
2	4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチルピロリジン－2（S）－カルボキサミド	１６
3	4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝－アミノ｝－2（R）－ヒドロキシ－4－フェニル－ブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	３９
4	4（S）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	３００
5	1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－4（S）－	７４５

	（2－メチルプロピルオキシ）ピロリジン－2（S）－カルボキサミド	
6	1－{3（S）－{{N－（ベンジルオキシカルボニル）－バリル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－N－tert－ブチル－4（R）－（2－メチルプロピルオキシ）ピロリジン－2（S）－カルボキサミド	180
7	4（R）－ベンジルオキシ－1－{3（S）－{{N－（ベンジルオキシカルボニル）バリル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－N－シクロプロピルピロリジン－2（S）－カルボキサミド	100
8	4（R）－ベンジル－1－{3（S）－{{N－（ベンジルオキシカルボニル）アスパラギニル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	48
9	4（S）－ベンジル－1－{3（S）－{{N－（ベンジルオキシカルボニル）アスパラギニル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	780
10	N－tert－ブチル－1－{2（R）－ヒドロキシ－4－フェニル－3（S）－{{N－（2－キノリニル－カルボニル）バリル}アミノ}ブチル}－4（R）－（2－ピリミジニルチオ）－ピロリジン－2（S）－カルボキサミド	4.7
11	N－tert－ブチル－1－{2（R）－ヒドロキシ－4－フェニル－3（S）－{{N－（2－キノリニル－カルボニル）バリル}アミノ}ブチル}－4（R）－{（3－ピリジニルメチル）－チオ}ピロリジン－2（S）－カルボキサミド	12
12	N－tert－ブチル－1－{2（R）－ヒドロキシ－4－フェニル－3（S）－{{N－（2－キノリニル－カルボニル）バリル}アミノ}ブチル}－4（R）－{（2、6－ジメチル－4－ピリミジニル）オキシ}－ピロリジン－2（S）－カルボキサミド	9.4
13	N－tert－ブチル－1－{3（S）－{{2、6－ジメチルフェノキシ）アセチル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－4（R）－（2－ピリミジニルチオ）－ピロリジン－2（S）－カルボキサミド	4.6
14	N－tert－ブチル－1－{3（S）－{{2、6－ジメチルフェノキシ）アセチル}アミノ}－2（R）－ヒドロキシ－4－フェニルブチル}－4（R）－{（3－ピリジニルメチル）－チオ}ピロリジン－2（S）－カルボキサミド	43

【0052】実施例13

式1の化合物の抗ウィルス効果をスクリーニングするために使用される下記の手順は、上記のハラダらにより既に報告されたHTLV－I形質転換された細胞を利用するプラクアッセイから改作した。HTLV－I形質転換された細胞は、それとともにHIVが細胞中で複製する速度が速いので使用した。

1．試験化合物をジメチルスルホキシド中に溶解して、濃度を5mg／mlとする。得られた溶液を使用まで4℃で貯蔵することができる。

2．得られた溶液をRPMI1640（ギブコラボラトリーズ、米国マサチューセッツ州ローレンス）中に希釈して、試験される最終濃度の4倍とする。RPMI1640中に希釈すると、この溶液は、4時間以内に細胞培

養アッセイにおいて使用される。

3．この4X溶液（50μl)を96ウェルの平底微滴定プレートの3部ウェルに添加した。RPMID（50μl)を対照ウェルにも添加する。

4．HEPES緩衝されたRPMI1640（pH=7.2）50μL中のC8166細胞（5×10⁴)、10%熱不活性化合物されたウシ胎児血清（FCS）、12.5μl／mlゲンタマイシン（完全培地）を全ウェルに添加する。

5．完全培地100μl中の50倍$TCID_{50}$のH9／HTLV－IIIBストック（50%FCS中の細胞培養上清として液体窒素中に保存される）を、全てのウェルに添加する。ウィルスストックの感染滴定量は、C8166細胞上の終点希釈により予め決定されたものと同じである。ストックの滴定量は、－193℃において保存した場合には、6～12時間安定である。

【0053】6．次いで、微滴定プレートを37℃、5%CO_2湿潤化されたインキュベーターの水平な棚上に72時間置く。

7．次いでプレートを外して、低電力相光学顕微鏡によ＊り各ウェル内のシンシチウムの中心を計測する。いくらかのシンシチウムの形成の証拠を示す細胞の各クラスターをシンシチウムの1中心として計測する。対照ウェルは、各ウェル毎に25～75のシンシチウムの中心を有する。

8．シンシチウム形成の阻害百分率は、下記式により算出する。

阻害（%）＝100×｛（#対照ウェル中のシンシチウム中心－#試験ウェル中のシンシチウム中心）／（#対照ウェル中のシンシチウム中心）｝

シンシチウム形成の50%阻害をもたらす試験化合物の濃度、即ちEC_{50}は、工程3の作用溶液の連続希釈技術を使用して、種々の濃度の試験化合物に対するシンシチウム形成の観察された阻害百分率をプロットすることによって決定される。下記表2において、本実施例のブラクアッセイから得られた式1の例示化合物のアッセイの結果が示されている。

【0054】

【表2】

表2

番号	化合物	EC50（nM)
1	4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝－アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	600
2	4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	600
3	1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）－バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－4（R）－（2－メチルプロピルオキシ）ピロリジン－2（S）－カルボキサミド	3000
4	4（R）－ベンジルオキシ－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）バリル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－シクロプロピルピロリジン－2（S）－カルボキサミド	900
5	4（R）－ベンジル－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝－アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	700
6	4（S）－ベンジル－1－｛3（S）－｛｛N－（ベンジルオキシカルボニル）アスパラギニル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－N－tert－ブチル－ピロリジン－2（S）－カルボキサミド	4000
7	N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニル－カルボニル）バリル｝アミノ｝ブチル｝－4（R）－（2－ピリミジニルチオ）－ピロリジン－2（S）－	250

	35	36
	カルボキサミド	
8	N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－｛（3－ピリジニルメチル）－チオ｝ピロリジン－2（S）－カルボキサミド	480
9	N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－｛（2、6－ジメチル－4－ピリミジニル）オキシ｝－ピロリジン－2（S）－カルボキサミド	390
10	N－tert－ブチル－1－｛3（S）－｛｛2、6－ジメチルフェノキシ）アセチル｝アミノ｝－2（R）－ヒドロキシ－4－フェニルブチル｝－4（R）－（2－ピリミジニルチオ）－ピロリジン－2（S）－カルボキサミド	250

【0055】式1のその他の化合物には下記のものがある：

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（フェニルスルホニル）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（2－ピリジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（4－ピリジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（4、6－ジメチル－2－ピリミジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－ピリジニルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－フェノキシピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－ピリジニルカルボニル）アスパラギニル｝アミノ｝ブチル｝－4（R）－フェノキシピロリジン－2（S）－カルボキサミド

N－シクロペンチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）ロイシル｝アミノ｝ブチル｝－4（R）－（フェニルスルホニル）ピロリジン－2（S）－カルボキサミド

【0056】1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）バリル｝アミノ｝ブチル｝－N－（1－メチルエチル）－4（R）－（2－ピリジニルチオ）ピロリジン－2（S）－カルボキサミド

N－シクロプロピル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）アスパラギニル｝アミノ｝ブチル｝－4（R）－（4－ピリジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－キノリニルカルボニル）イソロイシル｝アミノ｝ブチル｝－4（R）－（2－ピリミジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－ナフチルカルボニル）バリル｝アミノ｝ブチル｝－4（R）－（4、6－ジメチル－2－ピリミジニルチオ）ピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－ピリジニルカルボニル）イソロイシル｝アミノ｝ブチル｝－4（R）－フェノキシピロリジン－2（S）－カルボキサミド

N－tert－ブチル－1－｛2（R）－ヒドロキシ－4－フェニル－3（S）－｛｛N－（2－ピリジニルカルボニル）アスパラギニル｝アミノ｝ブチル｝－4（R）－（フェニルチオ）ピロリジン－2（S）－カルボキサミド

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